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EFFECT OF HYPOTHERMIA ON THE HEART RATE, THE ARTERIAL PRESSURE AND THE ELECTROCARDIOGRAM OF THE RAT

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The increasing use in medicine and surgery of reduced body temperature in the form of both general [1] and regional cooling [2] has aroused interest in the physiologic effects of hypothermia. The need for better methods of resuscitation and treatment of persons suffering severe reduction of body temperature through exposure has been amply demonstrated by the experiences of the armed forces in cold latitudes and by the incidence of injury from cold in shipwrecked personnel,[3] particularly in the North Atlantic. Fundamental understanding of the physiologic abnormalities produced by reducing the body temperature is necessary before effective therapeutic measures can be devised.

Smith [4] summarized the literature up to 1942 and presented in detail the effects of general hypothermia in man. He cited evidence which indicated that "refrigeration was not in itself a serious risk to the average patient." Too literal an interpretation should not be placed on this conclusion. The absence of anatomic evidence of specific myocardial damage attributable to the effects of low temperature is reassuring, but the mechanism of the "somewhat atypical form of circulatory failure which occasionally occurs" remains unexplained.

Experiments on animals have shown that nonhibernating mammals are unable to survive reduction of their body temperature below 13 to 18 C. (55.4 to 64.4 F.),[5] although Ariel and his co-workers [6] claimed to have observed survival in rabbits after reduction of their rectal temperatures to 10 C. (50 F.) by partial immersion of the animals in a cold water bath. Burton and Bazett [7] have pointed out the unreliability of rectal temperature as a satisfactory index of mean body temperature, particularly under conditions of measurement of that temperature in a water bath. Unless special precautions are taken, the participation of rectal blood vessels in thermovascular reflex responses and the physical nature of the "deep-to-surface" thermal gradients at the body orifices yield a rectal temperature appreciably below the mean body temperature.

Most investigators, from Walther [5a] in 1862 to Ariel [6] in 1943, have noted that respiration stops before the heart beat in fatal hypothermia and have suggested that the usual cause of death

The work reported was supported by grants from the John and Mary Markle Foundation and the Fluid Research Fund of the Stanford University School of Medicine.

1. Smith, L. W., and Fay, T.: Observations on Human Beings with Cancer Maintained at Reduced Temperatures, 75°-90°F, Am. J. Clin. Path. **10**:1 (Jan.) 1940.

2. Fay, T., and McCravey, A.: Pain Relief by Local and Generalized Refrigeration, Dis. Nerv. System **1**:209 (July) 1940. Herrmann, J. B.: Low Temperature Therapy of Malignancy, Connecticut M. J. **5**:721 (Oct.) 1941. Crossman, L. W.; Ruggiero, W. F.; Hurley, V., and Allen, F. M.: Reduced Temperature in Surgery: II. Amputations for Peripheral Vascular Disease, Arch. Surg. **44**:139 (Jan.) 1942. Allen, F. M.: Reduced Temperature in Surgery: III. Experiments on Pelvic and Abdominal Refrigeration with Special Reference to Traumatic and Military Surgery, Am. J. Surg. **55**:451 (March) 1942.

3. Webster, D. R.; Woolhouse, F. M., and Johnston, J. L.: Immersion Foot, J. Bone & Joint Surg. **24**:785 (Oct.) 1942.

4. Smith, L. W.: The Use of Cold in Medicine, Ann. Int. Med. **17**:618 (Oct.) 1942.

5. (*a*) Walther, A.: Beiträge zur Lehre von der thierscher Wärme, Virchows Arch. f. path. Anat. **25**: 414, 1862. (*b*) Simpson, S.: Temperature Range of the Monkey in Ether Anesthesia, J. Physiol. **28**:xxxvii (July) 1902. (*c*) Simpson, S., and Herring, P. T.: The Effect of Cold Narcosis on Reflex Action in Warm Blooded Animals, ibid. **32**:305 (May) 1905. (*d*) Britton, S. W.: Effects of Lowering the Temperature of Homeothermic Animals, Quart. J. Exper. Physiol. **13**:55 (Sept.) 1922. (*e*) Hamilton, J. B.: The Effect of Hypothermic States upon Reflex and Central Nervous System Activity, Yale J. Biol. & Med. **9**:327 (March) 1937.

6. Ariel, I.; Bishop, F. W., and Warren, S. L.: Studies on the Effect of Hypothermia: I. Acute Physical and Physiological Changes Induced by the Prolonged Hypothermic State in the Rabbit, Cancer Research **3**:448 (July) 1943.

7. Burton, A. C., and Bazett, H. C.: A Study of the Average Temperature of the Tissues, of the Exchanges of Heat and Vasomotor Responses in Man by Means of a Bath Calorimeter, Am. J. Physiol. **117**:36 (Sept.) 1936.

is respiratory failure. Hamilton [8] described the relationship between the heart rate and lowered body temperature in rats and in kittens. He presented electrocardiographic evidence of cardiac arrhythmias at low temperatures and offered the following opinion concerning their origin: ". . . the cardiac debilities are secondary to anoxemia produced by paralysis of the respiratory centers in the medulla." Woodruff,[9] on the basis of similar observations, came to the same general conclusion but reported evidence that in a few of his animals death resulted from failure of the circulation. Hook and Stormont [10] reported that in dogs and in cats there was a profound slowing of the heart with declining body temperature and that at about 22 C. (71.6 F.) rectal temperature there was a critical fall in arterial pressure. Talbott [11] pointed out that circulatory collapse and death may be precipitated during hypothermia by inducing peripheral vasodilation with externally applied heat, but they also stated that some patients died of cardiac failure during the maintenance of hypothermia.

While it is apparent that circulatory failure occurs in hypothermia, there are insufficient data in the literature to describe the course of events which brings it about. The experiments presented here were designed to study in detail the changes in the arterial pressure and the electrocardiogram of rats during reduction of their body temperature to lethal levels.

METHODS

Adult white rats of the Slonaker-Wistar strain were maintained at ordinary laboratory temperatures on a stock diet of Purina fox chow and tap water. The animals were prepared for the induction of hypothermia by the administration of sodium pentobarbital, 37.5 mg. per kilogram, given intraperitoneally. Any surgical procedure, such as insertion of a tracheal cannula or isolation of an artery for direct measurement of arterial pressure, was performed during the most profound anesthesia. In order to avoid undue depression of the central nervous system by the combined action of cold and the anesthetic, the animals were allowed to recover from the maximal effects of the anesthetic before any reduction of their body temperature was attempted. A brief study on adult rats of both sexes showed that there is considerable variability in the response to intraperitoneal injections of 37.5 mg. of sodium pentobarbital per kilogram. The mean sleeping time for a series of 20 rats was ninety-five minutes ± 10.62. In practice an interval of fifty minutes between time of injection of the anesthetic and the beginning of cooling was usually satisfactory, although a few animals required a little ether to control violent shivering and voluntary movements.

The rats were cooled by placing them on a coil of 5/16 inch (0.8 cm.) copper tubing which carried cold water circulated through it from a second coil placed in the cold chamber of a refrigerator. The large heat capacity of this system made it possible to obtain adequate rates of cooling without reducing the surface temperature of the coil below about 7 C. Removal of heat was facilitated by destroying the insulating effect of the rat's hair by wetting it with glycerin in the region in contact with the brass plate. The rectal temperature was measured in some experiments with a mercury thermometer and in others with an iron-constantan thermocouple and a recording potentiometer. The bulbs of the thermometers or the thermocouple tips were always inserted to a depth of 6 to 7 cm. Possible inaccuracies arising from point temperature recording from the thermocouples were avoided through the use of a brass collar (15 mm. long by 3.5 mm. in diameter) cemented to the tip of a small rubber catheter and held in firm contact with the thermocouple junction where it emerged from the lumen through the side aperture. This arrangement permitted the recorded temperature to approximate closely the mean temperature of a large segment of bowel rather than that of a single point.

Electrocardiographic studies were made with the three conventional leads connected to a Sanborn Stethocardiette and Cardioscope. Thus interval observations of the electrical activity of the heart could be made as frequently as desired, without need for photography, which requires time for processing of bromide paper, except when permanent records were desired for further study.

Direct measurement of arterial pressure in rats with low body temperature is attended by unusual difficulties caused by the greatly shortened clotting time and the tendency of the violent shivering movements to increase clotting in or near the cannula as the result of trauma. The use of a specially designed cannula [12] and the intravenous injection of heparin, 20 mg. per kilogram of body weight, just before arterial cannulation were measures helpful in maintaining a patent recording system. A modified Hürthle manometer was used for recording the arterial pressure. The chamber of this instrument changes less than 0.2 cc. in volume over the maximal range of pressures encountered in these measurements. When sodium citrate was used as the anticoagulant, the introduction of even this small amount of an 8 per cent solution into the circulation during the decline of arterial pressure was sufficient to produce slowing of the heart and disturbances of rhythm. Sodium thiosulfate in 50 per cent concentration was found to be the most satisfactory anticoagulant.

RESULTS

The Influence of Temperature on the Heart Rate.—The slowing of the heart rate which

8. Hamilton, J. B.; Dresbach, M., and Hamilton, R. S.: Cardiac Changes During Progressive Hypothermia, Am. J. Physiol. **118**:71 (Jan.) 1937.

9. Woodruff, L. M.: Survival of Hypothermia by the Dog, Anesthesiology **2**:410 (July) 1941.

10. Hook, W. E., and Stormont, R. T.: Effect of Lowered Body Temperature on Heart Rate, Blood Pressure and the Electrocardiogram, Am. J. Physiol. **133**:334 (June) 1941.

11. Talbott, J. H.: Medical Progress: The Physiologic and Therapeutic Effects of Hypothermia, New England J. Med. **224**:281 (Feb. 13) 1941.

12. Crismon, J. M.: A Cannula with Obturator for Use in Direct Arterial Pressure Measurements on Small Animals, to be published.

accompanied lowering of the body temperature was a change of remarkable uniformity (mentioned by Hamilton [8]). Figure 1 illustrates the relationship when heart rate is plotted against rectal temperature. The observations of Clark [13] showing a curvilinear relation of rate to temperature were obtained on the isolated rabbit atrium. Over the range of rectal temperatures from 13 to 35 C. (55.4 to 95 F.) the coefficient of correlation, derived from data on 12 animals, was 0.95, with 95 per cent confidence limits of 0.925 and 0.971. With rectal temperatures above 35 C. (95 F.) and below 16 C. (60.8 F.) much greater variability of the heart rate was encountered than

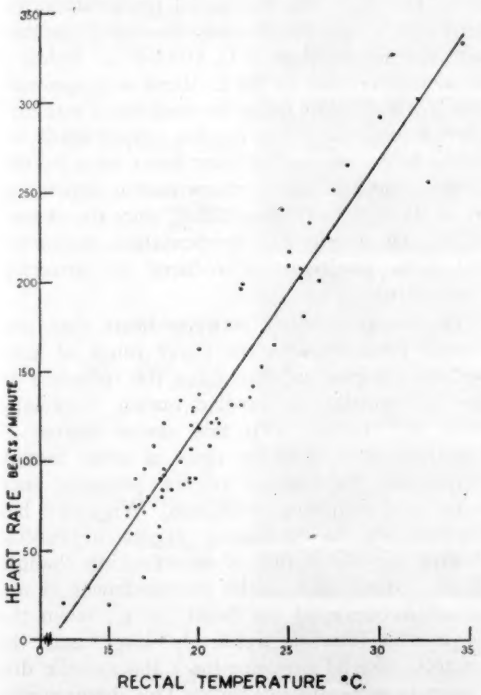

Fig. 1.—Relation between the heart rate and the rectal temperature in rats during hypothermia.

in the intervening ranges. With the upper range of temperatures the variability arose out of individual differences in response of the cardioregulatory reflexes. With the lower ranges determinations of heart rate were rendered less reliable by the appearance of various types of arrhythmia, usually culminating in complete block.

Since the relationship described was linear on a simple centigrade temperature scale, neither the Arrhenius type of expression used by Crozier [14] nor the methods proposed by Bělehrádek [15] for describing the influence of temperature on various biologic processes would improve on the present method of expression. The smooth curves obtained by treating the data according to the Arrhenius method or the Bělehrádek method require complex forms of analysis. It is interesting that on an Arrhenius plot, the data from our experiments yield a curve of about the same shape as that presented by Stier for the influence of temperature on heart beat frequency in immature mice.[16] Without arbitrarily drawn, confusing straight lines, it is impossible in the Arrhenius plots of either my data or those of Stier and Pincus to identify any abrupt changes in slope or to justify drawing a straight line for any portion of the curves. (See Ponder's [17] discussion of Hoagland's paper.)

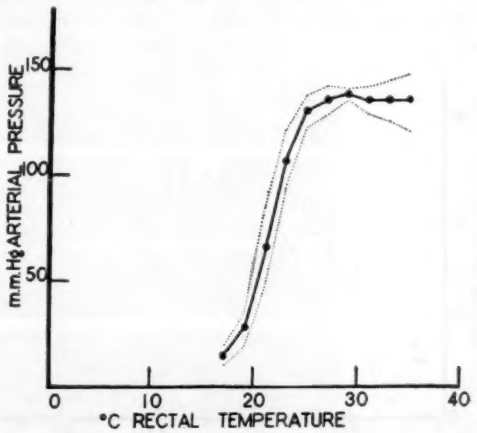

Fig. 2.—Changes in arterial pressure with declining rectal temperature in rats during hypothermia. The solid line shows the mean values for 9 animals; the dotted lines, the standard error of the means.

The Influence of Low Body Temperatures on Arterial Pressure.—Figure 2 presents a graph constructed from data on 9 rats illustrating the relation between arterial pressure and rectal temperature of cooled rats. The arterial pressure tended to rise until the rectal temperature had

13. Clark, A. J.: The Effect of Alterations of the Temperature upon the Functions of the Isolated Heart, J. Physiol. **54**:275 (Dec.) 1920.

14. Crozier, W. J.: On the Thermal Increment for the Locomotion of a Diplopod, J. Gen. Physiol. **7**:123 (Sept.) 1924.

15. Bělehrádek, J.: Temperature and Living Matter, Berlin, 1935.

16. Stier, T. J. B., and Pincus, G.: Temperature Characteristics for Heart Beat Frequency in Mice, J. Gen. Physiol. **18**:491 (March) 1935.

17. Ponder, in discussion on Hoagland, H.: Some Pacemaker Aspects of Rhythmic Activity in the Nervous System, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1936, vol. 4, p. 276.

fallen to about 29 C. (84.2 F.) and then declined slightly until the rectal temperature was between 24 and 21 C. (75.2 and 69.8 F.). Further reduction of the rectal temperature was associated with marked lowering of arterial pressure, at a rate approximating 15 mm. of mercury per degree C. This critical fall in arterial pressure with decrease of rectal temperature agreed well with similar observations on cooled rats and dogs reported by Hook and Stormont.[10] The rather large standard deviation in the values measured at higher rectal temperatures may be attributed to the considerable variability in the initial levels of arterial pressure and the differences among the animals with respect to the intensity of their shivering response. It was noted that the period during which the arterial pressure increased coincided with maximal shivering. In the animals in which complete atrioventricular block developed, it never appeared until after the arterial pressure had reached levels below 80 mm. of mercury.

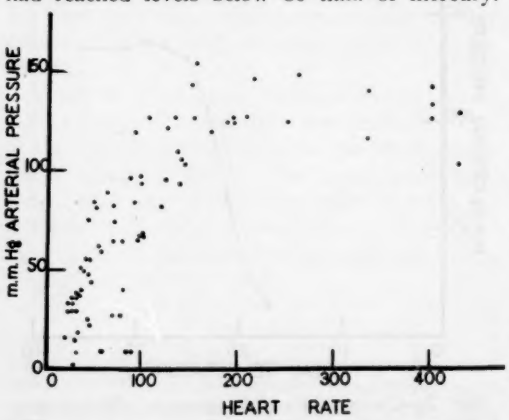

Fig. 3.—Influence of the heart rate on the arterial pressure during hypothermia. Data from simultaneous measurements of arterial pressure and electrocardiograms on 9 animals.

The increased cardiac metabolism[18] and the reduced coronary perfusion under these circumstances both contribute to local asphyxia. Wiggers[19] has reported the occurrence of cardiac arrhythmias in animals during progressive anoxia.

The Relation Between Arterial Pressure and Heart Rate in Hypothermia.—Figure 3 presents the relation between arterial pressure and heart rate in cooled rats. The rise in arterial pressure with slowing of the heart, which persisted until the rate had declined to about half that at normal body temperature, occurred during the phase of vasoconstriction and vigorous shivering early in the induction of hypothermia. Thus, during the period of maximal metabolic activity the increased venous return, facilitated by shivering, and the increased peripheral resistance combined to increase the cardiac output and the arterial pressure.

Continued reduction of the body temperature resulted in a decrease and finally in a cessation of the shivering response. Relaxation of skeletal muscle tonus followed the arrest of shivering, usually by the time the temperature had reached 20 C. (68 F.). At this rectal temperature the heart rate was approximately one-third the rate normally measured at 37 C. (98.6 F.). Below a rectal temperature of 20 C. there was approximately linear relationship between heart rate and arterial pressure. The cardiac output could no longer be maintained at slow heart rates by the familiar mechanism of compensation depending on augmented ventricular filling, since the venous return, on which this compensation depended, had been progressively reduced as shivering disappeared.

The linear relation between heart rate and arterial pressure with the lower range of temperatures serves to emphasize the influence of the bradycardia on cardiac output, especially since the animals with this severe degree of hypothermia showed no signs of other factors contributing to lowered arterial pressure, such as reduced peripheral resistance. Wiggers[20] has summarized the successive events in cardiac slowing and the nature of the resulting changes in cardiac output. Under circumstances of impaired nutrition of the heart (e. g., when the diastolic volume is relatively large and the diastolic arterial pressure low) the systolic discharge is reduced in volume. The abnormalities responsible for the reduced systolic discharge include the more gradual and longer isometric contraction, the lower pressure maximum and the shortened systolic ejection phase.

Wiggers[19] came to the conclusion that the circulatory failure observed in progressive anoxia is cardiac in origin without evidence of peripheral failure. Thus, whether low temperature alone or early cardiac asphyxia precipitated by respiratory failure becomes the crucial factor in collapse of the circulation in hypothermia, there seems to be little doubt that reduced cardiac output is the ultimate cause. The extent to which (*a*) the reduced filling of the heart and (*b*) the reduced

18. Starling, E. H., and Visscher, M. B.: The Regulation of the Energy Output of the Heart, J. Physiol. **62**:243 (Jan.) 1927.

19. Wiggers, C. J.: Cardiac Adaptations in Acute Progressive Anoxia, Ann. Int. Med. **14**:1237 (Jan.) 1941.

20. Wiggers, C. J.: The Pressure Pulses in the Cardiovascular System, New York, Longmans, Green & Company, 1928.

systolic ejection each contribute to the failure of the circulation in the cooled rats has not been determined. However, the frequent occurrence of pulmonary edema observed in the present experiments and in similar experiments by other workers [21] and the pronounced dilatation of the right ventricle and the pulmonary and splanchnic engorgement seen at autopsy in animals killed by reduction of their body temperature suggest that inadequate emptying of the heart rather than inadequate filling is the dominant factor leading to circulatory failure.

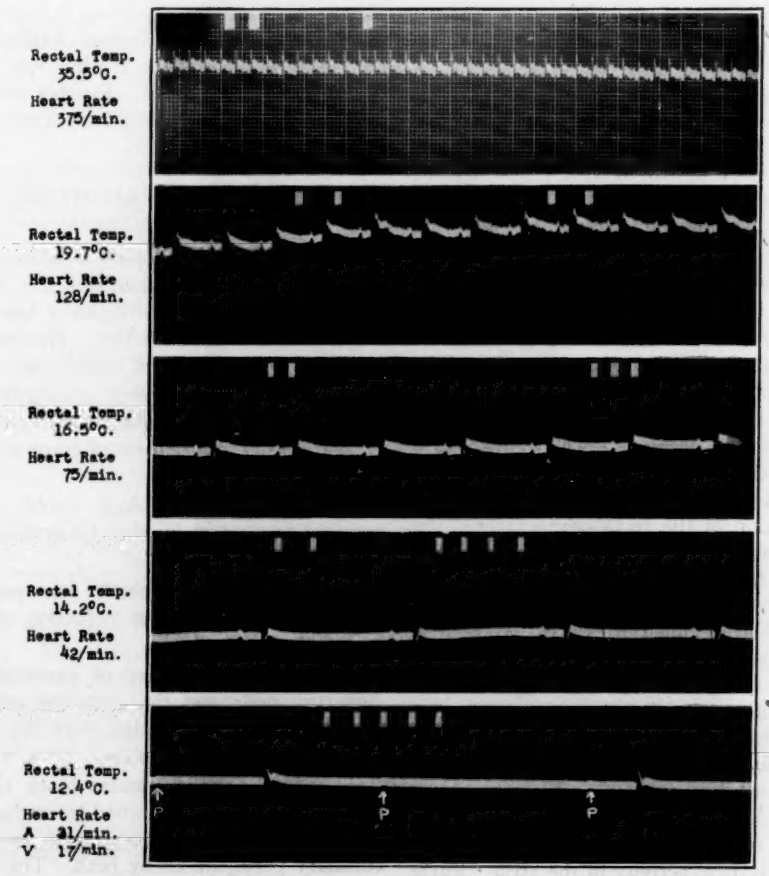

Fig. 4.—Electrocardiographic changes (lead II) in a rat cooled to 12.4 C. (54.2 F.).

The Effect of Low Body Temperature on the Electrocardiogram.—Typical changes in the contour of the electrocardiogram during the decline of rectal temperature are illustrated in figure 4. The electrocardiograms of anesthetized rats taken with rectal temperatures between 32 and 38 C. (89.6 and 100.4 F.) were similar to those of other small mammals with comparably rapid heart rates.[22] The P, R and T waves were upright in all three leads. The amplitude of the galvanometer excursions was greatest in lead II, where the R wave reached about 0.5 millivolts from the isoelectric line. When the excursion had progressed about halfway on the downward limb of the R wave, the T wave began. The raised RT segment thus produced is commonly seen in the electrocardiograms of small mammals with rapid heart rates and appears to be associated with the extremely brief interval into which all of the events of the cardiac cycle are compressed. Evidence for this view is found in the change produced in the RT segment as the heart rate slowed with declining body temperature. With reduction of the body temperature,

21. Walther.[5a] Simpson.[5b] Britton.[5d] Hamilton.[5e]

22. Zoll, P. M., and Weiss, S.: Electrocardiographic Changes in Rats Deficient in Vitamin B_1, Proc. Soc. Exper. Biol. & Med. **35**:259 (Nov.) 1936. Oppenheimer, E.: Elektrokardiographische Studien an kleinen Warmblütern, Ztschr. f. d. ges. exper. Med. **28**: 96 (Feb.) 1922.

the RT segment became less elevated, until with heart beat frequencies between 50 and 80 per minute the downward tendency of the excursion led to the development of prominent S waves. However, similar development of S waves may be associated with changed time relationships similar to those described by Nahum, Hoff and Kaufman.[23]

In experiments uncomplicated by early cardiac failure, the voltage of all parts of the electrocardiogram increased as the rectal temperature declined, but after severe circulatory failure (usually at 16 to 17 C. [60.8 to 62.6 F.]) the voltage diminished.

The slowing of the heart was associated with slowing of the spread of excitation throughout the heart. The lengths of the PR interval and the QRS complex increased at a proportionate rate, as indicated by the straight line relation obtained on log log plots of these intervals against length of cycle.

The Effects of Hypothermia on the Site of Origin and Atrioventricular Conduction of the Cardiac Impulse.—The P wave, which is upright in all three leads of the electrocardiogram of the normal rat, tended to become at first biphasic and then inverted in direction as the rectal temperature declined. The temperature at which the direction of the wave first became altered was variable, depending somewhat on the rate of reduction of the rectal temperature. In none of the animals' tracings was the P wave biphasic with temperatures above 25 C. (77 F.), but it was almost invariably so by the time the temperature had declined to 17 C. (62.6 F.). In a few instances brief periods were noted during which the P wave was entirely inverted. Complete obliteration of the P wave occurred invariably before cessation of electrical activity in the ventricles. Animals able to maintain spontaneous respiration at rectal temperatures below 17 C. (62.6 F.) showed regular ventricular rhythms of upper nodal origin without any evidence of electrical activity in the atria. Early failure of the respiration, on the other hand, was associated with disturbances in atrioventricular conduction. In some cases the complete atrioventricular block which ultimately developed was preceded by periods of varying degrees of partial block. Figure 5 presents an example of atrioventricular block and also illustrates the reestablishment of normal rhythm by the administration of artificial respiration. Artificial respiration was usually effective in restoring atrioventricular conduction if applied within a few minutes of the onset of atrioventricular block. The changes in contour and the disappearance of the P wave could not be restored to normal by this maneuver, but they did respond to elevation of body temperature.

Rats anesthetized with pentobarbital but not cooled were placed in a closed chamber and permitted to rebreathe. Electrocardiograms made during the course of the asphyxia thus induced showed the development of partial and complete atrioventricular block, which was completely reversed by restoring a normal atmosphere to the chamber. Neither change in contour nor disappearance of the P wave was noted as a consequence of asphyxia. Further details of the relation of asphyxia to low body temperature will be reported elsewhere.

MECHANISM OF ARRHYTHMIA IN HYPOTHERMIA

The observations reported indicate that at least two separate mechanisms are involved in the production of abnormalities of location of the pacemaker and of conduction. Evidence for this view may be summarized as follows:

1. Atrioventricular block appeared in cooled rats only after severe depression of the arterial pressure, when impairment of coronary perfusion may be assumed.

2. Atrioventricular block could usually be restored to normal rhythm by artificial respiration.

3. Atrioventricular block was produced by asphyxia in rats without reduction of the body temperature.

4. Signs of depression of excitability of the sinoatrial node and the atria disappeared with increase of temperature but were not affected by artificial respiration.

Thus, the atrioventricular block observed in cooled rats may be attributed to cardiac asphyxia produced by failure of respiration, by inadequate coronary perfusion or by both. The changes in location of the pacemaker, indicated by changes in contour and disappearance of the P wave, appear to be related closely to changes in temperature.

Barcroft[24] reported that electrocardiograms taken on hibernating marmots at rectal temperatures between 0 and 5 C. (32 and 41 F.) showed slow ventricular complexes, frequently irregular in rate, and were entirely lacking in signs of atrial activity. Suppression of sinoatrial discharges by low temperature is completely re-

23. Nahum, L. H.; Hoff, H. E., and Kaufman, W.: Nature of the S Complex of the Electrocardiogram, Am. J. Physiol. **136**:726 (July) 1942.

24. Barcroft, J.: Features in the Architecture of Physiological Function, London, Cambridge University Press, 1934.

versible. Marmots recover from hibernation without ill effects, and normal sinus rhythm has been reestablished in the hearts of rats cooled to rectal temperatures as low as 12.8 C. (55 F.) by permitting the temperature to rise gradually or by direct application of heat to the heart.

Cutts,[25] in discussing the transitions between normal sinus rhythm, ventricular escape, atrioventricular nodal rhythm and atrioventricular dissociation, summarized the conditions under which the atrioventricular node may become more irritable than the sinoatrial node and thus initiate this course of events. Of the conditions he mentioned, cooling of the sinoatrial node is the only one which might have obtained in the present experiments. Complete absence of atrial activity when the atrioventricular node was serving as the pacemaker in the hearts of the cooled rats could have occurred either because of depression of excitability in the atrium below levels enabling it to respond or because of identity in the rate of the sinoatrial and atrioventricular nodal discharge, the refractory phase of the atrium serving to prevent the latter from responding to excitation originating in the atrioventricular node. If the second of these two possibilities were responsible for the absence of P waves at low temperatures, one might expect to observe transition phases in which the temporal adjustments of the rates of discharge in the sinoatrial node and the atrioventricular node finally produced the interference type of block. Instead, the electrocardiograms taken at intervals during the cooling of the animals showed P waves which always preceded the QRS complexes by a distance which increased in proportion to the increasing length of the cardiac cycle.

The P wave, at first upright, became biphasic and then inverted and finally disappeared. It

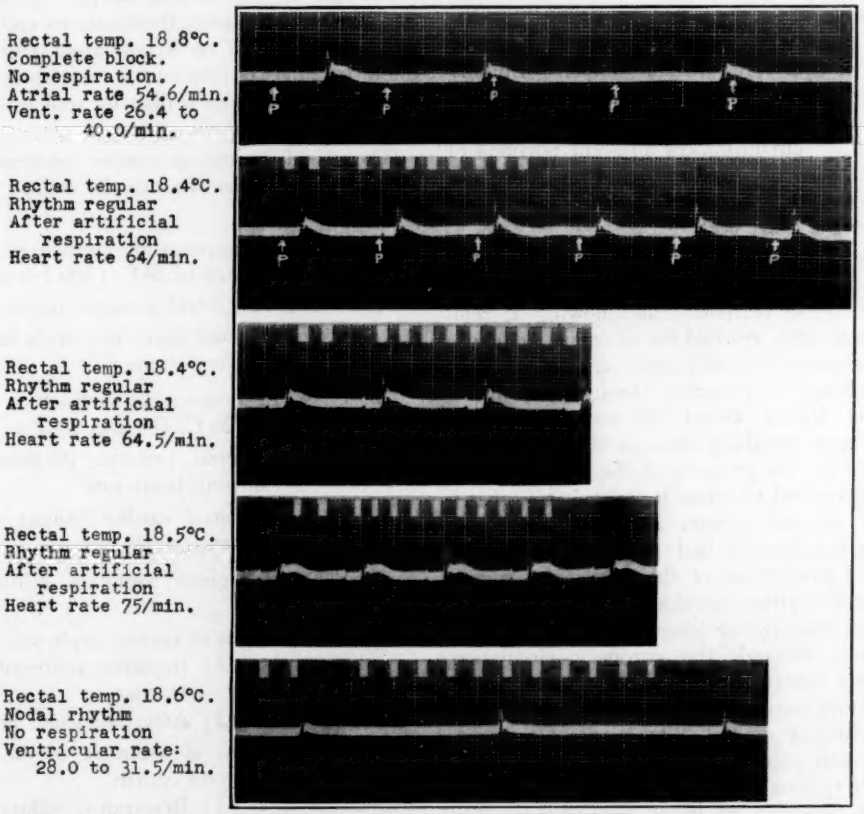

Fig. 5.—Effect of artificial respiration with 95 per cent oxygen and 5 per cent carbon dioxide on heart block in a rat during severe hypothermia.

25. Cutts, F. B.: The Transitions Between Normal Sinus Rhythm, Ventricular Escape, A-V Nodal Rhythm and A-V Dissociation: Report of Twelve Cases Including Seven Showing Interference Dissociation, Am. Heart J. **13**:451 (April) 1937.

has been suggested [26a] that changes in the contour of the P wave represent the results of a change in the location of the pacemaker within the atrium. Since the heart rate slows progressively, it is unlikely that the region serving as the new pacemaker has increased greatly in excitability; rather it is probable that the sinus node itself has for some reason diminished in excitability below the level in some other portion of the atrium. It has been demonstrated that small decreases of temperature at the sinoatrial node are capable of slowing the heart rate but that similar changes in temperature in surrounding cardiac tissues are without effect. Slightly greater reduction of temperature of the nodal tissues completely abolishes its discharges. Under these circumstances adjacent portions of the atria normally less excitable than the sinoatrial node are released and assume the role of initiating the heart beat.

In the rats undergoing reduction of their body temperature the cooled blood returning to the heart from the periphery, and flowing at relatively slow rates, reached the sinoatrial node at a lower temperature than it could have at any other time during its progress through the heart. Since in almost all of the experiments the animals were breathing room air at a temperature above 23 C., the progress of the blood through the lungs served to warm it somewhat so that it reached the left atrium at a slightly higher temperature than it had in the right atrium. The heat production of the ventricular muscle would still further increase the temperature of the blood reaching the tissues of the atrioventricular node through the coronary circulation. While no measurements of the differences in temperature were made, it may be suggested that the conditions of the experiments were consistent with successive depression of the most excitable regions of the heart, partially by reason of their exposure to lower temperatures than other parts and partly by reason of the inverse relation between the level of excitability and the sensitivity to cold.[26b]

COMMENT

The experiments presented here show that the circulatory failure occurring in rats subjected to marked reduction of their body temperature is closely related to the degree of cardiac slowing. Respiratory failure, described by many of the workers cited as the primary cause of death from hypothermia, did not occur until the body temperature was reduced to 15 to 21 C. (59 to 69.8 F.). In most cases respiratory arrest occurred with a rectal temperature between 16 and 18 C. (60.8 and 64.4 F.). The highest arterial pressure in the present series with a rectal temperature of 19 C. (66.2 F.) was 65 mm. of mercury, and the mean pressure with this temperature for the series was some 35 mm. lower. Irreversible damage to the respiratory center is a familiar phenomenon in the presence of even less severe impairment of the circulation in animals at near normal body temperatures.[27] It seems unreasonable, therefore, to ascribe the respiratory failure of hypothermia entirely to the direct effect of cold on the respiratory center. Circulatory failure is ordinarily well established before respiration fails.

The usual course of events culminating in death from hypothermia may be summarized as follows:

1. Phase of compensating circulatory adjustments, from 38 to 28 C. (100.4 to 82.4 F.)
   - (*a*) Peripheral vasoconstriction
   - (*b*) Slowed heart rate with increased stroke volume
2. Phase of progressive circulatory failure, from 29 to 20 C. (84.2 to 68 F.)
   - (*a*) Arterial pressure declining with slowing heart rate
   - (*b*) Reduced cardiac output through reduced stroke volume
3. Phase of regional asphyxia, below 19 C. (66.2 F.)
   - (*a*) Signs of cardiac asphyxia
     - (1) Impaired ventricular contraction
     - (2) Atrioventricular block
   - (*b*) Signs of asphyxia of the central nervous system
     - (1) Respiratory failure

SUMMARY

The effects of hypothermia on the heart rate, the arterial pressure and the electrocardiogram of rats cooled to lethal levels were investigated.

Both the heart rate and the conduction of the cardiac impulse were slowed by reduction of the body temperature. The relationship of the heart rate to the body temperature was linear over the range from 15 to 35 C. (59 to 95 F.), with a Q_{10} of 2.14, and had a high positive correlation. The slowing of conduction in the heart was proportional to the change in heart rate.

26. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, New York, Paul B. Hoeber, 1920, (*a*) p. 69; (*b*) p. 66.

27. Blalock, A.: Principles of Surgical Care: Shock and Other Problems, St. Louis, C. V. Mosby Company, 1940, pp. 129, 132, 137 and 144.

During the reduction of body temperature the arterial pressure increased as the shivering became maximal down to a rectal temperature of 29 C. (84.2 F.). Further reduction of temperature resulted in a decline of arterial pressure, at first gradual, until the temperature reached about 23 C. (73.4 F.), and then precipitous, as the temperature fell below 21 C. (69.8 F.). The relation between arterial pressure and heart rate became linear after the heart had slowed to about one-third the normal rate. Complete atrioventricular block was observed only after the arterial pressure had reached levels below 80 mm. of mercury.

Abnormalities of the P wave and complete atrioventricular dissociation were the most striking features at low temperatures. The arrhythmias were of two types: (*a*) sinoatrial block with shift of the pacemaker to other parts of the atria and finally the establishment of atrioventricular nodal rhythm; and (*b*) complete atrioventricular block. The first type was reversible by raising the body temperature slowly; the second may be corrected by administering artificial respiration or may disappear when the temperature rises slowly during recovery.

Respiratory arrest in hypothermic rats occurred only after the arterial pressure had fallen below 70 mm. of mercury. The circulatory failure preceding respiratory arrest was closely related to the degree of cardiac slowing.

Dr. Cathrine Crismon assisted in the study, and Prof. John Field II and Dr. V. E. Hall gave suggestions and criticism during the preparation of the manuscript.

RENAL AMYLOIDOSIS

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Renal amyloidosis, because of the signs and symptoms which it produces, lends itself to study more easily than does amyloidosis of almost any other abdominal organ. Consequently it has received more attention than similar involvement of other viscera.

During eleven years we have studied 468 cases of amyloidosis of various degrees. In 12 instances complete gross and microscopic studies of the kidneys were not made. In 379 (83.1 per cent) of the remaining 456 cases examination of the kidneys revealed deposition of amyloid.

TABLE 1.—*Diseases Underlying Renal Amyloidosis of Various Degrees*

	Underlying Disease							
Degree of Amyloidosis	Pulmonary Tuberculosis	Tuberculosis of the Bone	Genitourinary Tuberculosis	Empyema	Non-tuberculosis	Pulmonary and Other Tuberculosis	Tuberculosis of Bone and of Other Tissues	Empyema and Tuberculosis
Uremic.....	24 (14.9%)	7 (24.3%)	0	0	2 (40.0%)	43	15	13
Preuremic....	31 (19.0%)	3 (10.3%)	0	0	0	57	13	19
Moderate.....	38 (23.6%)	9 (31.0%)	1 (100%)	2 (100%)	2 (40.0%)	80	19	32
Minimal.....	68 (42.5%)	10 (34.4%)	0	0	1 (20.0%)	146	34	51
Total.....	161	29	1	2	5	326	81	115

ETIOLOGIC FACTORS

In each of our cases an underlying disease was present to account for the development of amyloidosis, tuberculosis being the causative factor in all but 5 cases. The latter group included 4 cases of chronic bronchiectasis and 1 of syphilis. This distribution is consistent with the universally accepted statement that tuberculosis is the most frequent cause of amyloidosis. Table 1 reveals that pulmonary involvement with or without extrapulmonary tuberculosis was the underlying disease in 326 cases (86.02 per cent).

The preponderance of pulmonary involvement is not unexpected, since in general our material for autopsy was composed largely of patients with chronic pulmonary tuberculosis. In 81 cases (21.1 per cent) tuberculosis of the bone alone or associated with some other tuberculous process was the basic disease. This shows only relative agreement with the expected distribution, since involvement of bone occurs in only 10 per cent of all cases in which autopsies are performed. We have found amyloidosis in 35 per cent of patients with tuberculosis of bone, a greater incidence than in patients with tuberculosis of any other organ system. Empyema, which has been considered as an important factor in the production of amyloid, was present in 115 cases (30.3 per cent), but since in all but 7 it was associated with tuberculosis elsewhere, a definite causal relationship cannot be established.

In the majority of patients the tuberculous process was in a progressive stage at autopsy. This does not corroborate Fishberg's [1] conception that amyloidosis is more apt to complicate tuberculosis in an inactive, afebrile stage than in a progressive one accompanied by high fever. In 5 of our patients with pulmonary disease there was no evidence of activity of the tuberculous process. In 3 others, although there was healing of the pulmonary lesions, there were residual postoperative thoracic sinuses. This fact does not confirm the usually accepted premise that when the underlying pathologic process undergoes healing, the amyloidosis undergoes regression. In a number of instances we have seen amyloidosis progress for several years after clinical healing of the underlying tuberculous process had taken place; in 1 case the interval was four years. In most of the patients renal amy-

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1. Fishberg, A. M.: Amyloid Nephrosis in Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939, pp. 407-420.

loidosis progressed until death from uremia resulted. It is interesting that as early as 1881 Dickinson [2] pointed out that it is frequently "dropsy" which induces the patient to seek medical advice. It is then only on careful inquiry that the nature of the preceding disorder becomes evident and the interval between the recovery from the original local disease and the appearance of renal symptoms is noted.

The duration of the underlying disease varied from five months to twenty-five years (table 2). In a slight majority (56 per cent) of the cases of minimal and moderate renal amyloidosis the underlying disease had existed less than three years. In 63 per cent of the cases in which renal amyloidosis led to uremia (53 cases) or preuremia (66 cases) the duration of the basic pathologic condition was three years or more.

TABLE 2.—*Duration of the Underlying Disease in Patients with Renal Amyloidosis*

Degree of Amyloidosis	Duration				Total
	6 to 11 Months	12 to 35 Months	3 to 10 Years	11 to 25 Years	
Uremic and preuremic	1 (0.8%)	43 (36.1%)	62 (52.1%)	13 (11.0%)	119
Moderate	5 (4.9%)	50 (49.0%)	46 (45.1%)	1 (1.0%)	102
Minimal	11 (7.0%)	80 (50.7%)	59 (37.4%)	8 (4.9%)	158

PATHOLOGIC CHANGES

Although Bell,[3] Dixon,[4] Raubitschek [5] and Rosenblatt [6] found the kidneys alone involved by amyloidosis in some cases, we have never found this to be true. In a few instances, however, we did observe moderate or severe renal amyloidosis accompanied by only minimal amounts of amyloidosis in the spleen and liver, the deposition limited chiefly to the walls of the blood vessels. A similar observation was made by Jennings, Altnow and Higgins.[7] In most instances the amyloid degeneration in the spleen and liver was more advanced than that in the kidneys.

Gross Appearance.—The appearance of the amyloid kidney depends on two factors: (1) the extent of the deposits of amyloid and (2) the amount of fibrosis present as a result of concomitant nephrosclerosis.

In the early stages of amyloidosis, there are no grossly visible changes which would lead one to suspect renal involvement, although the routine application of iodine may reveal mahogany brown areas in the region of the glomeruli. With progressive deposition of amyloid the kidney becomes firmer and acquires a waxy gloss. If the organ shows no evidence of fibrosis, the outer surface is smooth and waxy and cross sections appear bloodless. It is only in the kidneys of older persons showing varying degrees of nephrosclerosis that the outer surface is granular and the capsule is thickened and adherent.

One is justified from the data in table 3 to state that the weight of the kidney is no indication of the extent of renal amyloidosis unless the kidney is enlarged, since only in severe amyloidosis does the size of the kidney reflect the extent of deposition of amyloid. The largest kidney found in a woman weighed 325 Gm.; a kidney of this size was found in 2 persons, both of whom had severe renal amyloidosis. One of these patients died of amyloid uremia; the other was considered preuremic at the time of death. The largest kidney found in a man weighed 380 Gm. and showed severe amyloidosis. This patient died of amyloid uremia.

TABLE 3.—*Extent of Amyloidosis and Weight of Kidneys in Adult Patients*

Degree of Amyloidosis	Weight, Gm.				Total
	Below 150	150 to 199	200 to 299	300 or Over	
Uremic	3 (8.6%)	8 (22.9%)	19 (54.3%)	5 (14.2%)	35
Preuremic	3 (7.0%)	11 (25.6%)	24 (55.8%)	5 (11.6%)	43
Moderate	0	38 (70.3%)	16 (29.7%)	0	54
Minimal	1	53 (61.6%)	30 (34.9%)	2 (2.3%)	86

There were 3 instances in which severe amyloidosis occurred in small kidneys, weighing 95, 110 and 125 Gm. respectively. The patients died of uremia and showed, in addition to extensive amyloidosis, well developed nephrosclerosis.

Microscopic Appearance.—The first deposition of amyloid occurs in the glomeruli, usually in the region of the afferent vessels, although it is also demonstrable in the central portion of some glomeruli. We have designated this stage

2. Dickinson, W. H.: A Treatise on Albuminuria, ed. 2, New York, William Wood & Company, 1881, pp. 167-222.

3. Bell, E. T.: Amyloid Disease of the Kidneys, Am. J. Path. **9**:185-204 (March) 1933.

4. Dixon, H. M.: Renal Amyloidosis in Relation to Renal Insufficiency, Am. J. M. Sc. **187**:401-411 (March) 1934.

5. Raubitschek, H.: Ueber Nierenamyloidose, Virchows Arch. f. path. Anat. **182**:297-313, 1905.

6. Rosenblatt, M. B.: Amyloidosis and Amyloid Nephrosis, Am. J. M. Sc. **186**:558-567 (Oct.) 1933.

7. Jennings, F. L.; Altnow, H. O., and Higgins, G. K.: Renal Amyloidosis with Clinical Findings Suggestive of Polycystic Kidney, Ann. Int. Med. **10**: 1398-1405 (March) 1937.

"minimal renal amyloidosis." Hueter [8] and Bell [3] have shown that amyloid is first deposited along the inner surface of the basement membrane of the capillary. The deposits gradually separate the endothelium from the basement membrane and finally cause atrophy of both.

As amyloidosis progresses the amyloid clumps enlarge, fuse and cause compression atrophy of the neighboring visceral epithelium. In almost all instances the advanced process brings with it enlargement of the glomerulus and decrease in Bowman's space. This space may sometimes contain fluid, but usually it is empty. We have designated this stage "moderate renal amyloidosis."

In the advanced stage Bowman's capsule becomes progressively thickened by the development of hyalinized connective tissue, minimal amounts of amyloid sometimes being deposited within the latter. We believe that the thickening is a response to an irritative action of amyloid on the glomerulus.

Amyloidosis may progress until the capsular space is obliterated and the glomeruli appear entirely pink and homogeneous and are often enlarged one and one-half to two times their normal size. It is this stage of development that we observed in most of our patients who died of amyloid uremia. In a few cases, however, the capsular space was obliterated when there were only moderate deposits of amyloid in the glomeruli.

Like Koch,[9] we have never found glomeruli which underwent the transition from amyloid degeneration to hyalinization described by Fahr.[10] In kidneys showing nephrosclerotic changes, deposition of amyloid had also occurred in the glomeruli which were partially replaced by connective tissue, the amyloid being present in the nonfibrosed areas.

Amyloid is also laid down in the interstitial tissue just beneath the basement membrane of the tubules. In the medulla especially deposition may be extensive, causing separation of the renal tubules. It may also result in atrophy of the tubular epithelium due to compression and finally in disappearance of the tubules.

Two characteristic changes take place in the tubules in progressive amyloidosis: (1) atrophy and (2) dilatation. Our observations agree with those of Bell [3] that tubular atrophy is conspicuous in advanced amyloid disease and is almost always associated with obstruction of glomeruli by amyloid.

Tubular dilatation is a frequent occurrence in moderate and advanced renal amyloidosis and is almost a constant characteristic of kidneys of persons whose death was due to uremia. Casts are often present within the tubules; sometimes red and white blood cells and fibrin are also present. It has been pointed out by Koch [9] and Fahr [10] that while there were many casts in the kidneys at autopsy, during life these patients had few casts in the urine. Our data do not confirm this observation (table 9), although, in general, the number of casts is not commensurate with the amount of albumin.

A number of authors believe that in some instances casts are so numerous that they may obstruct most of the tubules and thus produce uremia (Fahr,[10] Bell,[3] Mark and Mosenthal [11]). We have been impressed by the consistent obliteration of the capsular spaces in the kidneys of all persons with uremia by deposits of amyloid. The obliteration is usually caused solely by deposition of amyloid, although in glomeruli in which nephrosclerotic changes have taken place slight or moderate deposition may suffice. We consider the obliteration of the capsular spaces throughout the kidney as the sole cause of uremia. Like Noble and Major [12] as well as Dixon,[4] we believe that advanced renal insufficiency is due to obliteration of the capillary bed in the glomerulus by deposition of amyloid beneath the basement membrane.

We examined slides of tissues from the kidneys of all patients in the series (379) for evidences of uremia and were able to make a correct diagnosis in every instance without previously knowing the clinical course of the patient. In 12 other cases (18 per cent), we diagnosed uremia, but, while the clinical data were consistent with the diagnosis of amyloid nephrosis, the chemical laboratory studies did not confirm the diagnosis of uremia.

Only occasionally have we observed an isolated cast giving a positive amyloid stain with methyl violet (methylrosaniline chloride). Similar observations were made by Raubitschek [5] and by Noble and Major.[12] Saleeby [13] found a positive-

8. Hueter, C.: Ueber Amyloid der Glomeruli, Centralbl. f. allg. Path. u. path. Anat. **19**:961-965 (Dec.) 1908.

9. Koch, F.: Vergleichende klinische und pathologisch-anatomische Untersuchungen zum Morbus Brightii, Krankheitsforschung **4**:321-348 (May) 1927.

10. Fahr, T.: Amyloidnephrose, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1934, vol. 6, pt. 2, pp. 835-843.

11. Mark, M. F., and Mosenthal, H. O.: Kidney Function and Uremia in Renal Amyloidosis, Am. J. M. Sc. **196**:529-539 (Oct.) 1938.

12. Noble, J. F., and Major, S. G.: Renal Insufficiency in Amyloid Disease, Arch. Path. **8**:762-774 (Nov.) 1929.

13. Saleeby, E. R.: The Question of the Existence of Amyloid Casts, J. A. M. A. **84**:344-345 (Jan. 31) 1925.

staining tubular inclusion body in sections of kidney in 1 of 50 cases but doubted that it was a cast and concluded that the occurrence of amyloid casts in the urine was doubtful.

Klebs [14] stated that one could not deny the possibility of amyloids passing into the urine from the kidneys, and after observing the occasional positive-staining casts within the tubules we concluded that if some of the casts were amyloid in character they would appear as such in the urine. In a series of 8 cases of renal amyloidosis we collected the urine at the time of autopsy. A paraffin section of the urinary sediment was made, as is done with pleural and peritoneal fluids, and the tissues were stained with methyl violet (methylrosaniline chloride). If amyloid casts are formed, they should be excreted in the urine and should be readily detected as such—an easy test for the diagnosis of renal amyloidosis. However, in none of our cases was a positive result obtained, although the kidneys of the patients from whom the urine was collected showed minimal to severe amyloidosis.

CLINICAL SYMPTOMS

Changes in Blood Pressure.—The blood pressures recorded in table 4 represent the average ranges during the last three to four months of life exclusive of terminal and postoperative pressures. Such readings were made in 144 cases.

The presence of a large number of patients with low blood pressures in our series is in agreement with the statement of Altnow, Van Winkle and Cohen [15] that hypotension is a frequent symptom in persons with renal amyloidosis. Fishberg [1] rightly says that it is, of course, obvious that the cachectic condition of most patients with renal amyloidosis tends to inhibit the maintenanee of hypertension and the development of cardiac hypertrophy, even if the essential factors for their production are present. Severe amyloidosis of the adrenal glands may have influenced the low blood pressures in all groups, particularly in the patients with uremia or with preuremic conditions, in whom amyloidosis of this organ as well as of the kidney was frequently extensive.

Whether or not they died of uremia, more than half of the patients had blood pressures within normal limits. The 3 patients with minimal or severe renal amyloidosis and elevated blood pressures had hypertensive heart disease.

Edema.—In table 5 the degree of amyloidosis is shown in relation to the presence or absence of edema. Of 339 patients for whom the data were available, edema of various degrees was observed in 196. As is to be expected, edema was most frequent and most severe in patients with the greatest amount of renal amyloidosis, while it was most frequently absent from persons with minimal renal involvement. Fahr,[16] on the other hand, stated that there can be no talk of a parallel between the severity of the glomerular changes and the occurrence of edema. He stated the belief that edema in persons with renal amyloidosis was extrarenal in origin.

TABLE 4.—*Blood Pressure and Extent of Amyloidosis*

Degree of Amyloidosis	Systolic / Diastolic	Blood Pressure, Mm. Hg: 100 or less / 70 or less	110 to 140 / 70 to 90	140 to 150 / 90 to 100	Over 150 / Over 110	Total
Uremic		9 (29.1%)	18 (58.1%)	2 (6.4%)	2 (6.4%)	31
Preuremic		11 (37.9%)	15 (51.7%)	3 (10.4%)	0	29
Moderate		13 (38.2%)	20 (58.8%)	1 (3.0%)	0	34
Minimal		18 (36%)	30 (60.0%)	1 (2.0%)	1 (2.0%)	50

TABLE 5.—*Edema and Extent of Amyloidosis*

Degree of Amyloidosis	Degree of Edema: Minimal	Moderate	Marked	None	Total
Uremic	9 (18.7%)	13 (27.1%)	22 (45.8%)	4 (8.4%)	48
Preuremic	12 (22.2%)	17 (31.3%)	19 (35.2%)	6 (11.3%)	54
Moderate	31 (32.3%)	13 (13.5%)	9 (9.4%)	43 (44.8%)	96
Minimal	43 (30.5%)	3 (2.2%)	5 (3.5%)	90 (63.8%)	141

Of the 5 persons with severe edema and minimal amyloidosis, 2 had cardiac decompensation and the remaining 3 had huge livers with massive depositions of amyloid.

14. Klebs, E.: Die allgemeine Pathologie, Jena, Gustav Fischer, 1889, vol. 2, pp. 164-182.

15. Altnow, H. O.; Van Winkle, C. C., and Cohen, S. S.: Renal Amyloidosis, Arch. Int. Med. **63**:249-275 (Feb.) 1939.

16. Fahr, T.: Beiträge zur Frage der Nephrose, Virchows Arch. f. path. Anat. **239**:32-40, 1922.

Edema in most cases occurred one month or less before death (table 8). Holten [17] made a similar observation in his cases. From this we may conclude that it is usually a terminal event. All patients who had edema for long periods had massive edema, although many of those in whom it occurred only during the last few weeks of life were extremely edematous also.

LABORATORY STUDIES

In many of the cases in our series insufficient laboratory examinations were performed; therefore complete correlation of data for all tests for all patients is not possible. Data were incomplete not only for patients with minimal amyloidosis but for those who had uremia. For the latter the pathologic conditions observed and usually the clinical course were compatible with uremia, but sufficiently complete laboratory examinations to support the diagnosis were lacking. However, at least one of the laboratory tests discussed was performed on every patient, and each of the tests will therefore be considered separately. All determinations unless otherwise specified were made within four months or less of death.

TABLE 6.—*Reaction to Congo Red Absorption Test in Patients with Renal Amyloidosis*

Degree of Amyloidosis	Amount of Congo Red Absorbed: 50 per Cent or Less	60 to 89 per Cent	90 to 99 per Cent	100 per Cent	Total
Uremic	1	3	3	29	36
Preuremic	1	0	5	44	50
Moderate	3	1	2	36	42
Minimal	4	8	3	29	44

Congo Red Test.—In table 6 the results of 173 congo red tests are recorded. Only the cases in which the dye was injected not more than three months before death are listed, with the exception of those in which repeated tests done more than three months before death showed repeated 100 per cent absorption of the dye. Lipstein and Auerbach [18] previously established 90 or 100 per cent absorption of the congo red dye as constituting a positive result if the test is performed according to the method accepted by the American Trudeau Society.[19] In 151 (87.8 per cent) of the congo red tests performed, a positive result was obtained. This result is contradictory to the opinion of Rosenberg [20] that the test is of no appreciable value in establishing the diagnosis of renal amyloidosis.

Of the 4 persons with uremia who absorbed less than 90 per cent of the dye, 2 were given the test two and three months before death, when there may have been an insufficient amount of amyloid present in the body to give a positive test. The other 2 were tested within one month of death, but they had only minimal depositions of amyloid in organs other than the kidney. Most of our false negative results were obtained in cases in which the deposits of amyloid were minimal or moderate. In a recent study we have found that the reaction to the test depends on the total amount of amyloid throughout the body, particularly in the liver, and not on the amount of amyloid in the kidney alone. In general, but not always, the quantity in the kidney reflects the quantity in the other organs.

Serum Proteins.—Determinations of total serum protein were made for 105 patients (table 7). For patients listed as having equal amounts of albumin and globulin the values of the two proteins were approximately the same; some of them might be placed in the "reversal" group, but for the sake of conservatism, only absolute reversals were listed under that heading.

Thirty-eight and nine tenths per cent of the patients with reversal of the albumin-globulin ratio and 34.5 per cent of those in whose serum the amounts of albumin and globulin were equal died of amyloid uremia (loss of albumin in the urine). In most of the other cases in which reversal occurred, it was again due to loss of albumin in the urine but there was not sufficient renal damage to constitute uremia or preuremia.

We have assumed the normal range of the total serum proteins to be 5.1 to 8.0 Gm. per hundred cubic centimeters. We used a minimum somewhat lower than that usually considered as normal because we have found that, in general, in tuberculous patients the total proteins are lower than in other patients, whether or not amyloidosis is present.

In 20.4 per cent of the patients with uremia or preuremia the amount of total serum protein was less than 5.1 Gm. per hundred cubic centimeters (table 7). It is surprising that so many patients in this group (43 patients, 79.6 per cent) had total protein values of 5.1 to 8.0 Gm., considering the amount of albumin they were spilling. It is also interesting that so many patients without evidence of uremia had reduced

17. Holten, C.: Nephritis Caused by Tuberculosis, Acta med. Scandinav. **61**:107-142, 1924.

18. Lipstein, S., and Auerbach, O.: An Evaluation of the Congo Red Test for Amyloidosis, Quart. Bull., Sea View Hosp. **2**:120-126 (Jan.) 1937.

19. American Trudeau Society: Report of the Committee on Standard Laboratory Procedure; Minimal Laboratory Standards, Am. Rev. Tuberc. **45**:103 (Jan.) 1942.

20. Rosenberg, M.: Zur Klinik der Amyloidniere, Deutsche med. Wchnschr. **99**:101 (Jan. 16) 1931.

total blood proteins although they were losing little or no albumin in the urine.

Tests of Renal Function.—The statement of Raubitschek [5] that there is nothing in the urinary data which is characteristic of the renal changes in amyloidosis was not entirely confirmed in our study. As renal amyloidosis progresses definite changes occur in the urine which, while not pathognomonic for the condition, are characteristic of nephrosis and may often be the first signs which lead to the diagnosis of amyloidosis. The changes include the appearance of albumin and casts in the urine and disturbance of the concentrating power of the kidneys. We have usually found red cells in the urine at some time during the course of the illness, particularly during the more advanced stages. Their presence constitutes a point of differentiation between true nonamyloid and amyloid nephrosis.

Albuminuria: Table 8 lists the data regarding albuminuria for 287 patients, those with renal tuberculosis being excluded. There was albumin in the urine of 264 (92 per cent). In a series of cases comparable to ours Rosenblatt [6] found an incidence of 82.3 per cent, and he rightly concluded that albuminuria occurring in a patient with amyloidosis is usually indicative of renal involvement.

TABLE 7.—*Serum Proteins of Patients with Renal Amyloidosis*

Degree of Amyloidosis	Albumin-Globulin Ratio			Total Serum Protein, Gm./100 Cc.					
	Normal	Equal	Reversed	3-4	4.1-5.0	5.1-6.0	6.1-7.0	7.1-8.0	8.1-9.0
Uremic	8	10	7	1	2	11	9	1	1
Preuremic	13	10	6	2	6	10	9	2	0
Moderate	16	5	3	1	0	12	10	2	0
Minimal	21	4	2	1	2	5	13	5	0
Total	58	29	18	5	10	38	41	10	1

TABLE 8.—*Albuminuria in Patients with Renal Amyloidosis*

Degree of Amyloidosis	Degree of Albuminuria				
	None	Trace	Small Amount	Large Amount	Total
Uremic	1 (2.2%)	1 (2.2%)	5 (10.9%)	39 (84.7%)	46
Preuremic	0	1 (1.8%)	7 (11.9%)	51 (86.3%)	59
Moderate	10 (15.8%)	13 (17.1%)	23 (30.3%)	28 (36.8%)	76
Minimal	23 (21.7%)	47 (44.3%)	22 (20.8%)	14 (13.2%)	106

The presence in our series of 34 cases of renal amyloidosis without albuminuria verifies the assertion that there are cases of amyloidosis of the kidneys in which no albumin appears in the urine (Senator,[21] Herringham [22] and Litten [23]). However, in 23 of these cases the amyloid involvement of the kidneys was minimal; in 10 it was moderate, and in 1 severe.

Thirty-eight patients excreted large amounts of albumin persistently for six months or more before death. Thirty-five (92 per cent) of these died of uremia or with preuremia. The remaining 3 had moderate renal amyloidosis without uremia. From these data one may conclude that any patient with renal amyloidosis who excretes large amounts of albumin in the urine persistently for more than six months probably has severe renal amyloidosis. These observations are similar to those of Altnow, Van Winkle and Cohen [15] but contrary to those of Bell,[8] who found no close relationship between the degree of albuminuria and the extent of amyloid infiltration in the kidneys.

There were 3 patients, 2 who died with uremia and 1 with preuremia, who had no albumin or only traces in the urine before death. One of these was a patient who died soon after admission and for whom a single analysis was made. The other 2 had excreted larger amounts for several months, but the content of albumin in the urine diminished before death.

TABLE 9.—*Excretion of Urinary Casts by Patients with Amyloidosis*

Degree of Amyloidosis	Hyaline Casts Only	Granular Casts Only	Both Hyaline and Granular Casts	No Casts	Total
Uremic	13 (27.1%)	4 (8.4%)	19 (39.6%)	12 (24.9%)	48
Preuremic	22 (37.9%)	1 (1.7%)	20 (34.5%)	15 (25.9%)	58
Moderate	15 (19.2%)	6 (7.7%)	14 (18.0%)	43 (55.1%)	78
Minimal	16 (12.2%)	9 (6.9%)	5 (3.8%)	101 (77.1%)	131

Urinary Casts: Table 9 lists the incidences of casts in the urine according to the degree of amyloidosis. Only hyaline and granular casts

21. Senator, H.: Die Erkrankungen der Nieren, Vienna, A. Holder, 1902, pp. 346-369.

22. Herringham, W. P.: Kidney Diseases, London, Oxford University Press, 1912, pp. 348-354.

23. Litten, M.: Zur Lehre von der amyloiden Entartung der Nieren, Berl. klin. Wchnschr. **15**:313-317 (June 3); 335-339 (June 10) 1878.

were considered, since waxy casts were too infrequent to be significant. In 214 cases casts were found in the urine, and the degree of correlation between the extent of amyloidosis and the presence of casts is striking. Of the patients with minimal renal amyloidosis, 30 (22.9 per cent) had urinary casts; of those with moderate amyloidosis, 35 (44.9 per cent) had casts and of those with preuremia or with uremia 74.1 per cent and 75 per cent respectively had casts.

Table 10 reveals that 16 (43.2 per cent) of the patients who died of uremia excreted urinary casts continuously for six months or more before death. Nine (21.4 per cent) of those with preuremia spilled casts for a like period.

TABLE 10.—*Interval Between Appearance of Symptoms and Death*

Interval, Months	Edema		Albuminuria		Casts	
	Patients with Uremia	Patients with Preuremia	Patients with Uremia	Patients with Preuremia	Patients with Uremia	Patients with Preuremia
1 or less	26	23	2	16	5	12
2	3	14	8	12	6	9
3	2	2	2	7	1	5
4 to 5	5	2	7	9	8	8
6 to 11	3	2	13	7	6	5
12 to 24	3	2	7	3	6	3
Over 24	0	0	6	5	4	1
Total	42	45	45	59	36	43

Urinary Concentration: The Mosenthal concentration test was performed for 65 patients (table 11). For many patients phenolsulfonphthalein and Fishberg concentration tests were performed also, but since these tests gave results similar to those obtained by using the Mosenthal technic they are not recorded. Forty-two (87 per cent) of the 48 persons who died of uremia or with preuremia had deficient power of renal concentration. One hundred per cent of those who died of uremia who had had tests performed within three months of death had inadequate renal function.

In almost all cases in which impairment of the ability to concentrate urine occurred it was severe, the specific gravity being fixed at 1.003 to 1.006, with the evening output of urine greater than 900 cc.

Fourteen (33.3 per cent) of the 42 patients with uremia or preuremia who had deficient concentration had the defect for six months or more before death. Of the patients with uremia or preuremia 38.9 per cent had large amounts of albumin and 31.6 per cent had casts in the urine for similarly long periods before death (table 8). Renal damage is, therefore, manifested by the excretion of albumin in the urine, deficient concentrating power in the kidney and the presence of casts in the urine, all at about the same time, although the loss of albumin is likely to come first. This observation is interesting in view of Rosenblatt's [6] statement that urinary signs, other than albuminuria, are of no significant diagnostic value and that renal concentration is generally unimpaired in persons with renal amyloidosis.

Nonprotein Nitrogen in Blood: Table 12 lists data for 162 patients for whom the amount of nonprotein nitrogen in the blood was determined, the last examination before death being the one recorded. For the 6 patients who are listed as having died of uremia with normal amounts of nonprotein nitrogen in the blood, no determination was made less than six weeks before death. The results, therefore, are not unexpected since in 19 patients (63.3 per cent) who died of uremia and who had increased nonprotein nitrogen, the elevation first appeared within one month or less before death. Many of these had repeated examinations, but the level of the nonprotein nitrogen did not begin to rise until the last few weeks. In 4 patients the level of the nonprotein nitrogen in the blood was continuously elevated for seven months or more before death.

The patient with minimal renal amyloidosis who had over 100 mg. of nonprotein nitrogen per hundred cubic centimeters of blood had bilateral renal tuberculosis and died of uremia from that cause and not of amyloid uremia. The data for this patient are not included in that for patients with amyloid uremia.

TABLE 11.—*Time of Onset of Impairment of Renal Concentration as Indicated by the Mosenthal Test*

Interval Between Onset of Disability and Death, Months	Degree of Amyloidosis			
	Uremic	Preuremic	Moderate, Without Uremia	No Amyloidosis
1 or less	5	7	2 (1)	0 (2)
2	1	5 (1)	0	0
3	4	0	1	1 (1)
4 to 5	1 (2)*	5 (1)	0	1 (2)
6 to 11	0 (1)	3	1 (1)	0 (1)
12 to 24	3 (1)	3	1 (3)	0
Over 24	3	2	0	0
Total	17	25	5	2

* The figures in parentheses indicate the number of patients with normal renal concentration according to the Mosenthal test.

Of the 2 patients with preuremia who had 51 to 100 mg. of nonprotein nitrogen per hundred cubic centimeters of blood, 1 died of tuberculous meningitis, the other of chronic pulmonary tuberculosis.

Cholesterol in Blood: Determinations of blood cholesterol were made in 76 cases. An increase in the cholesterol content of the blood was observed in 18 cases, in 14 of which the patient

had uremia or preuremia (table 13). However, the values obtained in the majority (68 per cent) of the determinations for patients with nephrosis were within normal limits, in contrast to the high values usually obtained for patients with nonamyloid nephrotic syndromes (Leiter[24]). The highest level of cholesterol, 425 mg. per hundred cubic centimeters, occurred in a patient who died two months later of amyloid uremia. The nonprotein nitrogen at the time of the cholesterolemia was within normal limits.

TABLE 12.—*Content of Nonprotein Nitrogen in the Blood of Patients with Amyloidosis*

Degree of Amyloidosis	Blood Nonprotein Nitrogen, Mg./100 Cc.				
	Below 40 (Normal)	41 to 50	51 to 100	Over 100	Total
Uremic	6 (17.1%)	3 (8.6%)	10 (28.6%)	16 (45.7%)	35
Preuremic	34 (87.2%)	3 (7.7%)	2 (5.1%)	0	39
Moderate	33 (94.4%)	3 (5.6%)	0	0	36
Minimal	49 (94.2%)	2 (3.8%)	0	1 (2.0%)	52

COMMENT

On the basis of our study of 379 cases of renal amyloidosis of various degrees of severity we have been able to follow the course of this disease from its onset to termination.

Renal amyloidosis generally develops as part of a generalized process in which there is also involvement of the spleen, the liver and the adrenal glands. In the majority of cases the extent of the amyloid involvement of the kidneys lags behind that of the liver and spleen. Most persons in whom renal amyloidosis develops die of the underlying disease, which in most instances is tuberculosis, or of the complications thereof. As a result a large proportion of patients with amyloidosis die with minimal or moderate renal involvement. In a relatively small proportion of cases (cases of "good chronic" pulmonary tuberculosis, tuberculosis of the bone and chronic pulmonary abscess) the amyloid process continues for a long period. In some instances amyloid degeneration progresses after the underlying disease has healed. It is in persons with these long-standing conditions that renal insufficiency usually develops, and these patients often succumb, not to the underlying disease, but to uremia. During progressive deposition of amyloid the typical clinical picture of nephrosis develops in a number of patients.

24. Leiter, L.: Nephrosis, Medicine **10**:135-242 (May) 1931.

In the early stages of renal amyloidosis there are often no signs or symptoms which would lead one to the diagnosis of this condition. Since the deposition of amyloid in the liver and spleen is usually more advanced, clinical observation of hepatomegaly or splenomegaly may lead one to suspect generalized amyloidosis. Under such circumstances a congo red test will usually establish the diagnosis. We found hepatomegaly and splenomegaly in only one third of our patients, and we do not consider these signs reliable aids in establishing the diagnosis. The congo red test is invariably positive in cases in which hepatosplenomegaly is observed because amyloidosis has developed to at least a moderate extent before it causes enlargement of these organs.

Sometimes in cases of minimal and usually in cases of moderate renal amyloidosis the signs and symptoms of renal involvement first lead one to the diagnosis of the condition. Our observations substantiate fully the statement of Altnow, Van Winkle, Maly and Williams[25] that if in the course of tuberculosis both albumin and casts appear in the urine in considerable amounts a diagnosis of renal amyloidosis may be entertained with the expectation that further study will confirm it. Diminished urinary concentration is almost always present when the presence of albumin and casts in the urine can be demonstrated.

TABLE 13.—*Content of Cholesterol in the Blood of Patients with Amyloidosis*

Degree of Amyloidosis	Blood Cholesterol, Mg./100 Cc.			
	Below 150	150 to 250	260 to 350	Total
Uremic	1 (4.6%)	14 (63.6%)	7 (31.8%)	22
Preuremic	0	17 (71.8%)	7 (28.2%)	24
Moderate	2 (16.7%)	9 (75.0%)	1 (8.3%)	12
Minimal	2 (11.1%)	13 (72.2%)	3 (16.7%)	18

In the early stages of renal amyloidosis a trace of albumin is present in the urine. The content of albumin usually remains low for a period of months and then gradually increases. Holten[17] emphasizes that in a number of cases it continues low until death, even if the latter does not take place for several months. In a few cases the amount of albumin excreted may increase rapidly in a relatively short period, an indication of rapidly progressive renal amyloi-

25. Altnow, H. O.; Van Winkle, C. C.; Maly, H. W., and Williams, L. E.: Renal Amyloidosis, Arch. Int. Med. **56**:944-975 (Nov.) 1935.

dosis. The presence of extensive albuminuria for any length of time is an indication of extensive amyloid degeneration of the glomeruli and of severe renal damage.

The loss of albumin in the urine causes a decrease in the total amount of protein in the blood, a change observed almost without exception in our cases of advanced renal amyloidosis. With this reduction there is a tendency toward inversion of the albumin-globulin ratio. Accompanying the albuminuria and generally increasing in proportion with it is the excretion of hyaline and granular casts. Simon [26] observed that the albuminuria preceded the appearance of casts in the urine by weeks or month

It is usually during the advanced stages of renal amyloidosis that the clinical picture of nephrosis appears. Patients with advanced renal amyloidosis formed only a small part of our series. We agree with Rosenblatt [6] that the term amyloid nephrosis is a misnomer if it is used to designate a distinct pathologic entity, since it is merely a form of renal involvement in which the deposition of amyloid has progressed to an advanced stage. The patient, in addition to having a low content of protein in the blood, has albuminuria and urinary excretion of casts, edema of the lower extremities and face and usually fluid of various amounts in the serous cavities. In most patients edema is a terminal event, usually occurring in the last month of life. However, the nephrotic syndrome may continue for a number of years without any clinical evidence of renal insufficiency. In 1 of our cases the nephrotic syndrome was present for four years before an elevation of the amount of nonprotein nitrogen in the blood occurred. Christian [27] described a case of amyloid nephrosis of almost three years' duration, while Linder, Maxwell and Green [28] described 1 of amyloid nephrosis of nine years' duration. The termination in these patients is usually death as a result of the underlying basic disease. In none of our cases was there evidence to support Rosenberg's [20] contention that the longer the duration of renal amyloidosis of the nephrotic form the greater the likelihood of the development of an amyloid contracted kidney.

In only a small proportion of cases does the patient survive the basic disease long enough for the amyloid process to continue until signs of renal insufficiency and eventually of uremia develop. Mark and Mosenthal [11] observed that impairment of renal function advances constantly in patients with amyloid disease of the kidney and that the longer the patient lives the more likely it is that renal insufficiency will develop. It is interesting to observe that although patients with progressive renal amyloidosis may live for years death ensues rather rapidly when renal insufficiency has developed. Sixty-three and three tenths per cent of our patients who died of uremia first showed an elevation of the amount of nonprotein nitrogen in the blood within one month of death. This indicates a fairly uniform deposition of amyloid within all of the glomeruli. With the closing of the capsular space retention of nitrogenous wastes develops rapidly.

Patients who died of amyloid uremia showed the clinical characteristics of this condition, that is, coma, uriniferous odor of the breath, edema and subfebrile temperature. In almost all instances patients who ultimately died of uremia had previously manifested a typical nephrotic syndrome.

Twenty-four of the patients who died of amyloid uremia had enlarged kidneys with a smooth surface, true amyloid kidneys. Noble and Major [12] described 2 cases of amyloid uremia in which the kidneys were unusually large and showed no evidence of contraction. They pointed out that in all references to this condition that they were able to find in the literature the kidneys are described as being shrunken. It is rather interesting that Zadek [29] during the same year (1929) independently pointed out that in spite of statements to the contrary in previous publications, uncomplicated renal amyloidosis may lead to fatal azotemia.

Although we found no instance of contraction of the kidney due to amyloidosis, such a condition has been described by Danisch,[30] Fahr [31] and Willer.[32] In the 2 cases described by Danisch there was also advanced arteriosclerosis of the kidneys. Never having observed fibrous transformation or replacement of amyloid tissue in the kidneys or any other organs, we doubt

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29. Zadek, E.: Ueber Urämie bei Amyloidniere, Klin. Wchnschr. **8**:249-252 (Feb. 5) 1929.

30. Danisch, F.: Ueber Amyloidschrumpfnieren, Verhandl. d. deutsch. path. Gesellsch. **20**:307-318, 1925.

31. Fahr, T.: Zur Frage der Amyloidnephrose und Amyloidschrumpfniere, Klin. Wchnschr. **10**:1205-1208 (June 27) 1931.

32. Willer, H.: Ueber Amyloidschrumpfnieren; unter besonderer Berücksichtigung des Kreislaufs, Frankfurt. Ztschr. f. Path. **46**:306-320, 1933.

the occurrence of contracted kidneys due to amyloidosis.

SUMMARY

The course, prognosis and pathology of renal amyloidosis have been studied, and various diagnostic criteria have been evaluated. In order of their approximate chronologic appearance these criteria are as follows: albuminuria, excretion of urinary casts, disturbance of renal concentrating power, lowering of serum proteins, reversal of the albumin-globulin ratio, edema and retention of the waste products of metabolism. The last two symptoms usually appear within the final month of life and together constitute an extremely bad prognostic sign. The blood pressure and the level of the blood cholesterol are of no particular diagnostic significance.

While renal amyloidosis is almost always present in patients with generalized amyloidosis, it is usually not the direct cause of death. Furthermore, patients may survive for long periods of time with the renal function impaired by amyloid degeneration and still succumb to the basic disease rather than to the renal damage.

Whether or not the patient succumbs to amyloid uremia depends on the patency of the glomerular capsular space. When this has been obliterated by depositions of amyloid, death from uremia is inevitable.

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GELATIN AS A SUBSTITUTE FOR PLASMA

OBSERVATIONS ON ITS ADMINISTRATION TO HUMAN BEINGS

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The intravenous administration of a solution of gelatin as a blood substitute for the treatment of clinical shock was first reported by Hogan [1] in 1915. However, this demonstration of the possible efficacy of gelatin solution was forgotten until the present need for an adequate substitute for plasma, brought on by the present war, stimulated renewed interest in the possibilities of this substance.[2] As a result of the recent increased interest gelatin is being studied more intensively. One of the important methods for evaluating any plasma substitute is to study its ability to relieve experimental shock in animals. However, the interpretations of data obtained from such experiments on animals are often complicated by many factors arising from the methods of producing experimental shock, and therefore conclusions from such experiments are not always applicable to the treatment of shock in human beings. This point has recently been stressed by Blalock.[3]

This study on human subjects was designed to obtain additional information regarding the value of gelatin as a plasma substitute and is part of a larger study undertaken to evaluate various macromolecular substances which have been proposed for the treatment of shock.

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From the Department of Medicine of Wayne University, College of Medicine, Detroit, and the Eloise Hospital.

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2. Ely, J. O., and Angulo, A. W.: J. Franklin Inst., 1943, no. 235, p. 197. Gordon, H.; Hoge, L. J., and Lawson, H.: Am. J. M. Sc. **204**:4, 1942. Grodins, F. S.: Federation Proc. **2**:17, 1943. Ivy, A. C.; Greengard, H.; Stein, J. F., Jr.; Grodins, F. S., and Dutton, D. F.: Surg., Gynec. & Obst. **76**:85, 1943. Kleinberg, W.; Remington, J. W.; Eversole, W. J.; Overman, R. R., and Swingle, W. W.: Am. J. Physiol. **140**:197, 1943. Little, J. M., and Wells, H. S.: ibid. **138**:495, 1943. Parkins, W. M.; Koop, C. E.; Riegel, C.; Vars, H. M., and Lockwood, J. S.: Ann. Surg. **118**:193, 1943. Taylor, N. B., and Waters, E. T.: Canad. M. A. J. **44**:547, 1941. Waters, E. T.: ibid. **45**:395, 1941. Wolfson, W. L., and Teller, F.: Am. J. M. Sc. **178**:562, 1929.

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METHODS

The solution used in these experiments was 5 per cent osseous gelatin in isotonic solution of three chlorides U. S. P. or in isotonic solution of sodium chloride U. S. P. The oncotic pressure of this gelatin solution was 70 mm. of mercury. It was pyrogen free, had a p_H of 7.2 and was prepared for intravenous administration by the Upjohn Company, Kalamazoo, Mich. In the course of these studies twenty different lots of gelatin solution were used.

The subjects in these experiments were patients with no detectable cardiovascular disease, and they were not in shock. Changes in plasma volume, urea nitrogen and amino acid levels in the blood, erythrocyte sedimentation rate, hemoglobin concentration, white cell count and results of urinalyses were observed at intervals following the intravenous injection of gelatin solution. The gelatin content retained in the serum and that excreted in the urine were also measured.

Determinations of plasma volume were made by the method of Gibson and Evans [4] as modified for the photoelectric colorimeter.[5] The blue azo dye T-1824, introduced by Evans, was reinjected for each determination. Sedimentation rates of the erythrocytes were measured by the Westergren technic.[6] Gelatin concentrations in the serum were calculated by multiplying the differences between the nitrogen content of the tungstic acid filtrate and that of the trichloroacetic acid filtrate of the serum by 5.25. Gelatin concentrations in the urine were calculated by multiplying the nitrogen content of the tungstic acid precipitate of the urine by 5.25. All determinations of nitrogen were made by the method of Pregl and Parnas-Wagner.[7] Determinations of the blood amino acids were made by a modification [8] of Sahyun's method.[9]

Fifty-six injections of gelatin solution were given to forty-five subjects during these experiments; the amounts given in the individual injections ranged from 450 cc. to 1,000 cc., and the rate of injection varied from 5.6 cc. to 19.2 cc. per minute. Gelatin solution was also administered to 3 moribund patients, and their tissues were subsequently examined histologically. Repeated injections of 500 cc. each were given to several persons during a two week period; each of 2 subjects

4. Gibson, J. G., and Evans, W. A., Jr.: J. Clin. Investigation **16**:301, 1937.

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7. Pregl, F.: Quantitative Micro-Organic Analysis, London, J. & A. Churchill, Ltd., 1937.

8. Krauel, K. K.: Personal communication to the authors.

9. Sahyun, M., and Goodell, M.: J. Lab. & Clin. Med. **24**:548, 1939.

received eight 500 cc. injections by the intravenous route, and 1 received an equal number of injections of 500 cc. each by the intrasternal route. A few subjects received two or three injections at eight to ten day intervals. To 50 patients gelatin solution was administered for the treatment of shock.

RESULTS

Effect of Gelatin Solution on the Plasma Volume.—Table 1 is a summary of the effect of gelatin solution on the plasma volume in 12 subjects for whom the increase in plasma volume was measured. Gelatin solution produced a significant increase in plasma volume in all patients, and increments of increase are expressed as per cent of volume of gelatin solution injected. In 5 subjects for whom the determination of plasma volume was repeated immediately after the infusion, the increase in plasma volume represented 51 to 68 per cent (average 58 per cent) of the volume of gelatin solution administered. Four hours after the infusion the increment of increase varied from 51 per cent to 84 per cent, the average being 70 per cent. Twenty-four hours later the average increase in plasma volume was 46 per cent of the volume of gelatin solution administered.

TABLE 1.—*Increase in Plasma Volume, Expressed as Per Cent of Gelatin Solution Injected*

Patient	Volume Injected, Cc.	Increase in Plasma Volume		
		Immediate	After 4 Hours	After 24 Hours
1	500	63.0	....	....
2	1,000	51.0	....	....
3	500	....	84.0	....
4	500	....	52.0	....
5	500	....	78.0	....
6	800	....	51.0	....
7	1,000	....	64.0	118.0
8	1,000	....	82.0	22.0
9	1,000	....	76.0	25.0
10	1,000	68.0	....	18.0
11	500	56.0	....	40.0
12	500	51.0	....	49.0
Average.....		58	70	46

TABLE 2.—*Gelatin Concentration in Serum, in Grams Per Hundred Cubic Centimeters*

Patient	Gelatin Injected, Gm.	Concentration					
		Immediately	After 2 Hr.	After 4 Hr.	After 6 Hr.	After 8 Hr.	After 24 Hr.
1	50	0.612	0.413	0.266	0.153	0.149	0.020
2	50	0.683	0.533	0.328	0.152	.....	0.107
3	50	0.437	0.384	0.342	0.269	0.250	0.137
4	50	0.712	0.543	0.389	0.313	0.247	0.061
Average.....		0.611	0.468	0.331	0.222	0.212	0.086

Disappearance from the Blood and Recovery in the Urine.—The disappearance of gelatin from the blood stream was studied in 12 patients. Table 2 shows the gelatin concentrations in grams per hundred cubic centimeters at intervals following the injection in 4 representative experiments. The concentration of gelatin decreased progressively from an initial concentration of 0.6 Gm. per hundred cubic centimeters to less than 0.1 Gm. twenty-four hours later. Four hours after the injection approximately 50 per cent of the gelatin had disappeared from the blood stream, although at the corresponding time the plasma volume was increased by 70 per cent of the injected volume. By the end of twenty-four hours 87 per cent of the gelatin had disappeared from the blood stream, although the average increase in plasma volume at the end of twenty-four hours was 46 per cent of the volume of gelatin solution injected.

The amount of gelatin recovered from the urine was measured for 8 persons, and representative data obtained from studies on 5 of these subjects are shown in table 3. Approximately 46 per cent of the gelatin injected was recovered in the first four hours. In the next twenty hours an additional 30 per cent of the injected gelatin was recovered. The total amount recovered in twenty-four hours was 76 per cent. The excretion of gelatin in the second twenty-four hour period was slight. No gelatin was detected in the urine after forty-eight hours. The average total amount of gelatin recovered in forty-eight hours was 81.3 per cent of the amount injected.

TABLE 3.—*Recovery of Gelatin from the Urine*

Patient	Gelatin Injected, Gm.	Gelatin Recovered In 4 Hr., Gm.	Per Cent	Gelatin Recovered In 24 Hr., Gm.	Per Cent	Gelatin Recovered In 48 Hr., Gm.	Per Cent
1	40.0	17.886	44.7	35.023	87.5	36.624	91.5
2	40.0	22.445	56.1	31.471	78.7	31.471	78.7
3	37.5	15.045	40.4	27.147	72.5	29.110	77.8
4	47.5	23.011	48.6	29.258	61.8	37.228	78.3
5	35.0	13.818	39.7	27.942	80.0	27.942	80.0
Average.....			45.9		76.0		81.3

Blood Urea Nitrogen and Blood Amino Acid Levels.—The levels of urea nitrogen and amino acids in the blood were measured at two hour intervals after the injection of gelatin solution into 15 subjects. No significant changes in these values were observed during the twenty-four hour period of observation.

Effect on Erythrocyte Sedimentation Rate.—The injection of gelatin solution uniformly produced a marked increase in the sedimentation rate of erythrocytes in the 12 subjects for whom it was measured. Characteristic data obtained from

studies on 4 subjects are shown in table 4. The increase in sedimentation rate paralleled the gelatin concentration in the serum and was approximately normal at the end of twenty-four hours.

Autopsy Material.—In the 3 moribund patients who received repeated injections of gelatin solution and whose tissues were later examined histologically, no pathologic changes were noted which might be attributed to the gelatin, nor was any evidence of retention of gelatin in the tissues observed.

Clinical Trial of Gelatin.—To 50 patients who were admitted to the hospital in varying degree of shock, gelatin solution was administered for therapy. For each patient satisfactory results were obtained, as manifested by elevation of the blood pressure and clinical improvement.

TABLE 4.—*Influence of Gelatin on the Erythrocyte Sedimentation Rate (Fall in Mm. in One Hour)*

Patient	Initial Rate	Rate After 2 Hr.	Rate After 4 Hr.	Rate After 6 Hr.	Rate After 8 Hr.	Rate After 24 Hr.
1	16	71	55	53	..	32
2	22	100	93	76	53	29
3	20	74	50	30	26	15
4	12	108	86	57	32	24

Detailed data on these patients will be presented in a later report.

Reactions.—No reactions were observed during or following any of the infusions. There were no elevations of temperature or chills, and all patients tolerated the infusions well. Examination of the urine revealed no casts, red cells or other evidences of renal irritation. No significant changes in white blood cell counts were observed, and the hemoglobin concentrations reflected only the changes in the volume of the circulating blood produced by gelatin solution. No reactions of sensitivity were noted in any of the patients who received repeated injections of gelatin solution.

COMMENT

From our observations it appears that gelatin solution effectively increases the plasma volume of the normal person and that the major part of this increase is maintained for at least twenty-four hours. The increases in plasma volume which occur after infusions of gelatin solutions compare favorably with those observed following intravenous injections of pectin solution and are greater than those which follow intravenous crystalloid infusions.[10] Although the 45 subjects observed in the physiologic part of this study were not in shock, the results of our clinical experience with the 50 additional persons who were in shock indicate that gelatin solution effectively increases the plasma volume and thereby corrects the major circulatory defect in this condition.

The increase in plasma volume following the injection of gelatin solution persisted longer than the presence of gelatin in the blood would indicate. It has been shown[11] that in normal man the total circulating proteins of the blood as well as the plasma volume increase after ingestion of large amounts of salt or sodium bicarbonate or injection of desoxycorticosterone acetate. It may be that with the increase in plasma volume following the injection of gelatin solution a similar increase in total circulating protein is responsible for the continued elevation of the plasma volume after the gelatin in the blood has decreased to negligible quantities. This is being investigated at present.

Information regarding the fate of gelatin when it is administered intravenously to man is incomplete, and therefore any data regarding the utilization, storage or excretion of this substance are important. The fact that there were no significant alterations in either the blood urea or the blood amino acid levels after the infusions of gelatin indicates that no appreciable metabolism of gelatin occurred. It is recognized that failure of the values of the blood urea and blood amino acids to rise after injection of gelatin solution is not complete proof that this substance is not metabolized, and additional studies to clarify this point are in progress. It may be that the 20 per cent of the injected gelatin which was not recovered in the urine is metabolized, but we have no evidence to indicate that this is so. The ability to recover approximately 80 per cent of the injected gelatin from the urine in forty-eight hours further suggests the likelihood that no appreciable metabolism of gelatin occurs. Histologic examination of the tissues of the moribund patients who received gelatin did not reveal any changes which might be attributed to the gelatin, nor was there any histologic evidence of retention of gelatin in the tissues.

The effect of gelatin on the sedimentation rate of erythrocytes raises the question of intravascular clotting as a possible complication of the use of gelatin solutions. Although the subjects were all carefully examined, no untoward symptoms in any way attributable to this phenomenon could be elicited.

10. Jacobson, S. D., and Smyth, C. J.: Proc. Soc. Exper. Biol. & Med. **50**:218, 1942.

11. Lyons, R. H.; Jacobson, S. D., and Neerkin, J.: To be published.

SUMMARY

A 5 per cent solution of purified bovine osseous gelatin was safely administered intravenously to 45 normal persons and to 50 patients in shock. Gelatin solution effectively increased the plasma volume for at least twenty-four hours in persons not in shock or suffering from any cardiovascular disease. Approximately 80 per cent of the injected gelatin was recovered from the urine in forty-eight hours. There was no evidence to indicate that gelatin solution administered intravenously was metabolized. We believe that gelatin fulfils many of the essential requirements of a substitute for human plasma and warrants an extensive clinical trial in the treatment of shock.

Miss Margaret Klein gave us technical assistance.

PRINCIPLES UNDERLYING STUDIES OF NUTRITION PERTAINING TO THE INFLUENCE OF SUPPLEMENTS ON GROWTH, PHYSICAL FITNESS AND HEALTH

WITH A COMPREHENSIVE BIBLIOGRAPHY OF THE STUDIES

REPORT BY THE COMMITTEE ON DIAGNOSIS AND PATHOLOGY OF NUTRITIONAL DEFICIENCIES, NATIONAL RESEARCH COUNCIL

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Studies on the effects of supplementary feeding bear on a topic uppermost in the minds of persons interested in public health. Urgently wanted is an answer to the question: Will proper additions to ordinary diet bring consequent improvement in nutrition which is reflected in increased growth, health and efficiency? This is not the same question as: Does a poor diet have an adverse effect on growth, health and physical performance? Nor is it the same as: Does improvement of a poor diet have a favorable influence on these functions and qualities? It is not restricted to supplementation of poor diets. "An ordinary diet" is a highly variable term, including a wide range in quantity and quality. Many of the studies on supplementation included diets that were poor; but many others were at least fair, if not good. These have been supplemented by either a natural food or specific nutrients, such as minerals and vitamins.

The type of study under consideration is distinguished by its objective. It may be completely quantitative with the subjects under constant supervision and control; but most often, for reasons of feasibility, it has not been. For the most part the aim of highly quantitative studies has been to demonstrate that the body needs some particular essential as judged by the effect on growth or to ascertain the requirement of an essential or to study the effects on metabolism. Such investigations have not been included. Rather, the subject pertains to those studies, whether highly supervised and controlled or not, having as their aim determination of the direct effect of supplementation on growth, physical performance and health.

Numerous studies have focused on the effect of a natural food supplement on the growth rate of children. Others have dealt with its effect on pregnancy and industrial absenteeism. Multivitamin and mineral supplements have been tested for their influence not only on growth but also on physical performance, psychologic responses, pregnancy and health of persons. On none of these points are the results entirely in agreement. Yet in the studies on the effect of a natural food supplement on growth, the results point preponderantly to an increased rate, and probably that relationship is most generally accepted. Again, the major part of the evidence on the effect of dietary supplementation on pregnancy indicates beneficial action. Here the results parallel those from animal studies, in which supplementation of diets has almost invariably yielded positive effects on growth and reproduction. Some of the studies on the effect of supplementation on the incidence of infection and of minor respiratory or gastrointestinal ailments in man have revealed a favorable influence, but the results have not been sufficiently uniform to gain as widespread acceptance as those on growth. Studies on the effects of supplements on physical performance have yielded contrary results which have led to opposing views. In some studies the supplement showed beneficial effects; in others, none. Thus discordance in results has come from studies on the subject made on human beings.

A comprehensive list of studies of the type under consideration has been brought together here into a bibliography (arranged chronologically) solely for convenience. While most of the studies are listed, none will be completely analyzed and reviewed. This is not a review of the literature on the subject. Rather, the conditions that frame any study will be enumerated and discussed, with appropriate examples from a few selected studies. Thus, such studies

as are mentioned are cited only as examples of some one principle or point, not for critical review of all their conditions or results. It is hoped that by such presentation of the principles the reader will be aided in making his own critical evaluation of any study.

No two studies are conducted under identical conditions. Therefore no detailed syllabus or protocol for a single study would be universally applicable. That would be a much too narrow approach, which would mislead the slavish or unwary investigator. Hence, this is not an outline of specific procedure setting forth an experiment under one set of conditions inapplicable to all others. That would be useful to very few people. Rather, it is an outline of principles applicable to all conditions and therefore for any investigator. It was not planned to provide the worker with a ready-made set of directions which would be generally unsuitable. Instead, application of the principles should enable him to set up his own study in accordance with his particular conditions.

The many studies on the subject have yielded seemingly contradictory and conflicting results. The report aims to show that when certain principles are borne in mind these seeming contradictions are resolved. It presents and explains these principles. In its application it should aid in the interpretation of the results already on record as well as of those to come. By the same token, these principles are to be kept in mind in planning and conducting such studies.

The discordance in results from studies with human beings is in contrast with the agreement in those with animals. It should be noted that the studies with animals have been conducted under terms and conditions which allowed effects to be manifested. Besides, there was much less variation in conditions within the group of animals. All the studies with human beings, however, have been carried out under different conditions, some of which were not conducive to allowing any effect to become manifest, and there was much more variation within groups.

In any study on human beings there are conditions in the population group under observation and terms of the plan which have a modifying and determinative influence on the outcome. They are: the index, methods and criteria for appraising nutritional status; the initial nutritional status of the subjects; the diet of the subjects; environmental and endogenous conditions conducive to deficiency states; the index, methods and criteria for appraising physique, physical performance and health; the initial status of subjects with respect to physique, physical performance and health; the selection of population groups for observation; the size of the population sample; the nature and potency of the supplement, and the duration of the study.

All these are variables which must be recognized, taken into account and subjected to control. Furthermore, they must be regarded not as isolated and detached items but in relation to each other. These conditions and terms, in combination, make up the frame determining the results of the study and the scope of its applicability. To learn exactly what the results of a study mean and whether a generalization can be established from them, it is necessary to examine the setting of the study in reference to all of these points. Both in planning a study and in analyzing and interpreting its results, these conditions are to be weighed.

In view of the existing confusion and controversy over the results in studies on man, it is advisable to consider the conditions which govern them. These are now to be examined in detail.

1. The indexes and methods which have been used for appraising nutritional status may be classified broadly into two groups according to their basis: growth and deficiency states. Actually, anything that is affected by nutrition may by a potential index of it. In the studies with supplements the aim has been to ascertain whether growth, immunity, resistance and efficiency are affected by them. From many studies on both human beings and animals, it is accepted that growth can be influenced by diet; therefore, it has been used as an index of nutritional status. The other bodily reactions are not in the same category.

An index of nutrition should permit initial status to be ascertained and changes in it to be followed. In many types of study it is necessary to know what the status is at the start; it is equally desirable to know what it is at the end in order to know whether and how it has changed. An accurate index should reflect nutritional status and its change. Growth has been used for both purposes. Both cross-sectional and longitudinal measurements of physique have been employed for the appraisal of nutritional status. Also, change in rate of growth, as shown by measurements in longitudinal studies has been used as an index of change in nutritional status.

Growth as an index of nutritional status has its limitations. It is only one manifestation of nutrition and not the most sensitive. It is neither the complete index nor the synonym of nutrition. As one manifestation, it is only part of the whole; conclusions about the whole cannot safely be

derived from the part. Optimum growth is not necessarily indicative of optimum nutrition. It is possible to have good growth and development of deficiency states. The latter may exist for a long time with no distinguishable interference with growth or effect on bodily measurements.

Likewise, change in rate of growth as an index of change in nutritional status from such sources as supplements also has its limitations. Although growth is only one aspect of nutrition, it is true that if its rate increases from a supplement it is assumed with some justification that nutritional status has improved. Yet other aspects of nutrition, such as deficiency states, may not have undergone corresponding improvement. While nutrition and its effects from diet are not manifested exclusively and completely in growth, conversely, growth is not exclusively and completely influenced or controlled by diet. If the rate of growth is not increased from a supplement, it does not necessarily mean that nutrition has not been improved. Nor does it necessarily mean that growth or nutritional status is already optimum. This fact puts restrictions on use of longitudinal growth as an index of change in nutritional status.

Not only is growth an inadequate index of nutritional status, but use of it in appraisal of status has the further drawback that the types of measurements, the available standards and the amount of deviation to be allowed for individual variation have been questioned. The many measurements, ratios and standards reflect the general dissatisfaction over them. Height and weight have been the most frequently used measurements. It is unfortunate that almost all experiments on animals and several studies on human beings have used only weight, for measurement of height as well as of other diameters might have added much to the knowledge of the effect of diet on body build. No satisfactory basis for establishing a standard has been found; hence the succession of standards, mostly arbitrary or statistical, have been open to criticism. As for allowable deviation from a standard, it is agreed that marked impairment in height or weight means poor nutritional status. But lesser deviations present difficulties in classification and appraising of individuals. Thus, the procedure falls down in the zone where it is most needed. Then, too, growth has still another limitation as an index; it operates only during one period of life. Beyond that period physique as a measure of nutrition applies to an aspect other than growth.

Some studies have used growth as the index of appraising initial nutritional status; others have used no particular index. With all its limitations, nevertheless, growth has value as an index when it is frankly poor or when the statuses of groups are to be compared in relative terms. Intentionally or unwittingly, in most studies on the effects of supplements growth as determined by measurements of height and weight has been taken as the index of change in nutritional status. For the purposes of such longitudinal studies its use is justifiable; but its limitations should be borne in mind in interpreting results and drawing conclusions. In later sections it will also be placed in the form of its end product, physique, in the same category with physical performance and health, where the effects on it will be considered regardless of its role as an index of nutritional status.

Choice of an index and methods for appraising nutritional status depends primarily on the object and terms of the study. Selection of an inadequate or inappropriate index and methods may have unfortunate consequences impairing the value of the study. It does not permit knowledge of true nutritional status either at the beginning or at the end of the study; thus it may not permit detection of any change in status or interpretation of results. In most instances appraisal of nutritional status in terms of presence or absence of deficiency states should be included. By such means nutritional status is more sensitively and reliably revealed. Furthermore, since not all impaired nutritional statuses improve at the same rate, the method should indicate the rate of response to be expected from an appropriate supplement. In one study the use of newer methods for detecting deficiency states allowed results to be analyzed and interpreted with conclusions that would otherwise not have been reached.

2. It is desirable to know the nutritional status of subjects at the beginning of a study, since it affects and may determine the results.

Initial status has a bearing on the outcome through the amount of its variation in the group under observation. When variation is great at the beginning, it is likely to be great in the results. The greater the variation the greater must be the average change in the group in studies such as those on supplements, if it is to be significant. When growth has been the index, studies with animals show an amount of variation considerably different from that in groups of children. Whereas a group of animals after a period on stock diet are brought to a more or less uniform state of deficiency for experimentation, a group of persons selected for study are not likely to show such a degree of

uniformity in their status. This difference holds true whether it is for signs of deficiency states or for height and weight as indexes of status. It should be borne in mind in planning studies on man or in interpreting their results.

Then, too, initial status is a controlling factor in the rapidity of change produced by supplements. Just as not all deficiency states respond with equal rapidity, so increase in growth or improvement in other respects may not always occur with the same speed. Such differences in rates of response may be viewed as depending on the character of the deficiency process.

Initial status has influence over the final results through determining the extent of potential change. The poorer the initial status, the greater would be the possible improvement from a proper supplement. Contrariwise, the better the initial status, the less would be the possible betterment. This relationship would hold whether it applied to recession of signs of deficiency states or to increase in rate of growth. Subjects in poor nutritional status would be expected to show the greatest response to appropriate therapy. Animals under experimentation are usually brought to a known severe status of impaired growth from which therapeutic response is always pronounced. In contrast, it is always more time consuming and less spectacular to accelerate their growth when they are only slightly below par. Witness the length of time required during its span of life for the well fed rat to surpass its previous records of growth to a slight extent. For human beings, as for animals, it is true that if subjects with pronounced underdevelopment of dietary origin are given a generous, adequate diet for a sufficient time, increase in weight will certainly result. But in mass studies on the effects of supplements on growth of children, the initial status of the subjects as determined by physical measurements has not generally been of considerable or extreme inferiority.

In such studies, as well as in comparable experiments on animals, the trend has been toward better and better initial status in subjects. Reflecting improvements in the stock diet, the weight curves of stock rats have increased over the years. The average heights and weights for age of children in school have increased by decades. It has been a slow process. This constant improvement in the status of the population presented a constantly improved initial status in studies. When several studies on the effects of supplements on the growth of children are arranged in chronologic sequence, the initial heights and weights for age in each project show a progressive increase.[1] These changes have been interpreted as indicating improved nutritional status and have been attributed to improved diet. This heightened initial status reduces the amount of further potential improvement. The change that can be effected by supplements is diminished. To demonstrate these slighter amounts of change in such situations has necessitated increasing attention to the details of plan and conduct of a study and application of statistical analyses to the data. In studies on human beings, in which variation within the group is greater, even greater attention to these details is demanded than in experiments on animals. If variation in initial status is high, indicating likelihood of equally high variation in the results, the study must be properly planned to allow slight changes to be detected. Thus, the plan of a study on improving fair or good nutritional status, whether measured by signs of deficiency states or growth and resolution of the results, is different from that of a study on correcting poor status.

Since the initial nutritional status of subjects influences the character of the results, knowledge of that status is necessary for planning a study and is valuable in the interpretation of the results. But in practice this information is generally neither determined nor known. In the reports of some studies it has been asserted that there was no evidence of any deficiency disease. But of forms of deficiency states other than the classic severe, acute form nothing is usually reported. On the basis of usual experience the prevalence of such states is likely. Too often human subjects are merely described as "normal." What is actually meant by that term is the usual in the observer's experience. But the usual for one observer may not be that for another. From "normal" may be inferred that the subjects are ambulatory, without major complaint, obvious severe acute deficiency state or organic disease. Unfortunately it implies too a certain homogeneity in the nutritional status of the group with every person in a satisfactory state. That is contrary to fact. Human beings are neither uniform nor entirely satisfactory in their nutritional status.

Knowledge of the nutritional status of subjects at the beginning of a study helps in the careful planning of it. This information allows decisions about the appropriate supplements or therapy to be given, suitable methods to follow any change, how long before it may be expected and whether it will be marked. Furthermore, it reveals the

1. Mann, 1926; Orr., 1928; Leighton and McKinlay, 1930; Bransby and others, 1944.

variation within the group and the maximum potential improvement that could be achieved. It is helpful in decisions on the size and composition of the population sample to be studied. To all these points it brings perspective. The studies on the relation of nutrition to senescence in animals exemplify this point. While conducting their biologic analyses of individual foodstuffs after the discovery of vitamins, McCollum and Simmonds in a series of papers (published in 1917 and 1919) pointed out that early onset of senescence was always associated with poor diets and poor nutrition. Rats only one fourth through their life span actually showed the characteristic appearance of senescence. Here the effects, not of inadequate versus supplemented diet, but of inadequate versus good control diet, were contrasted. These studies involving the experimental production of senescence and shortened life span, not postponement of it, presented the extreme of poor nutritional status. Differences between the two groups in growth and in longevity were marked. Signs of senescence were so pronounced as to be recognized by inspection, and that evidence was sufficient. Here the difference in status between experimental and control subjects was so great that a small sample was satisfactory. Later Sherman (1928 and 1930), investigated whether by improving the stock diet (actually by modification, though it amounted to supplementation) the good nutritional status of stock animals could be improved with effect on growth, senescence and longevity. Here the difference between the two groups would not be so striking as in McCollum's study or in the usual type of experiment on animals. The potential change was much less. It required a mass study with a large sample, a longer period of study and statistical analysis of the data. This comparison indicates how knowledge of initial status may guide the plan of study.

Knowledge of initial nutritional status is also important in interpreting the results of a study. Indeed, in analysis of data this knowledge may on occasion be necessary in order to bring out the difference between groups and to establish its significance. For example, in one study (Kohn, Milligan and Wilkinson, 1943) a difference between groups emerged only when the subjects were subgrouped according to nutritional status as ascertained by newer methods. It was stated that a group receiving the vitamin supplements gained significantly more in weight than did a group of controls classified as being deficient in vitamin A but otherwise comparable. Similarly, the supplemented group exhibited better performance in the endurance test than did control groups classed as being deficient in vitamin C alone and in both vitamins A and C. Unsatisfactory as was the basis of classification, the results suggest that even in a short period with a small sample differences from supplementation may become manifest when existing nutritional status is taken into account.

What is of further importance, the difference in initial status between subjects of various studies may be responsible for their seemingly contradictory results. In the zone of less impaired growth characteristic of the subjects in most studies on supplements, there have been appreciable differences in initial status between groups. Within the same age group, the subjects in the study of Mann (1926), in which milk as a supplement brought improvement in growth, were initially lighter and shorter on the average than those in several other studies.[2] Positive results in adequate time were to be expected in the former study, while less response to supplements within a limited period of time in the latter studies would be understandable. In comparing the results of studies, therefore, the initial status of the subjects must be kept in mind, for it may prevent premature and erroneous conclusions in reasoning by simple analogy.

Just as between nutrition and growth, a similar relationship appears to prevail between initial nutritional status and the magnitude of potential increase in physical performance. Several studies [3] have shown that adults subjected to deficient diets with induction of acute deficiency states suffered from easy fatigability and lowered muscular efficiency which were corrected by proper supplement, while a comparable number of adults maintained on an adequate diet without intervention of acute deficiency states showed within approximately the same length of time no demonstrable increase in recovery from fatigue or in muscular energy from a multivitamin supplement.[4] To avoid premature conclusions and misconceptions it is to be noted that these results on physical performance are being considered at this point only in relation to initial status. In all instances the sample was extremely small and the duration of the study was extremely short. In analyzing and interpreting the results of a study or in comparing the results of many studies, recognition of the relationship between initial status and amount and rapidity of potential

2. Leighton and McKinlay, 1930; Bransby and others, 1944.

3. Egaña and others, 1942; Johnson and others, 1942; Barborka, Foltz and Ivy 1943.

4. Foltz, Ivy and Barborka, 1942; Keys and Henschel, 1942.

increase in physical performance in response to supplements may obviate seeming contradiction.

Despite want of information on a relationship between initial status and increase in resistance to disease, the demonstrated influence of initial status on the potential increase in growth and physical performance from supplements strongly recommends that initial status should likewise be ascertained in studies on relation of nutrition to health.

3. The basic diet before as well as during the study may have a bearing on the results.

Variation in the nutritive value and quantitative adequacy of the basic diet from individual to individual within the group may contribute to the variation in the data. This variation in the dietary intake produces variation in its effects. Hence, part of the variation in the results with supplements arises from variation in the basic diet of the individuals. This variation is much less in experiments on animals, in which diet is controlled, than in studies with persons. In the former, rats from inbred stock with the same previous dietary history are subjected alike to a uniform basic diet. Here variation from the basic diet is at a minimum. In studies with human beings, the variation in basic diet within the group may be considerable. The greater this variation and therefore the greater the variation in its effects, the greater must be the average response to a supplement in order to be significant.

The basic diet in its nutritive quality or quantity exerts an influence over the final results through determining the extent of potential response from the supplement. It is possible that the diet may lack a nutrient which the addendum supplies. Here the diet is not supplemented but complemented. If the diet lacks a nutrient which the addendum does not supply, the full effect of the latter may be prevented. Or the basic diet may be relatively complete but capable of improvement by an addendum. Here the diet is supplemented. Then, again, the diet may need an addendum that complements and supplements. The more deficient the diet, the greater will be the contribution from an adequate supplement and the more pronounced will be the response to it. On the other hand, the more adequate the diet, the smaller will be the contribution and the less will be the effect from the supplement. For example, from statements in the report of Mann's study it is clear that the boys had previously been poorly fed. Milk was the test supplement given only to the experimental group. In contrast, in Fowke's study (1943) both experimental and control groups were receiving a good diet, including milk in school, while the former group was also receiving vitamins as a test supplement. As might be expected under these circumstances, the increase in growth from supplementation in the latter study is likely to be of less magnitude within a limited period of time.

Furthermore, a change in the basic diet prior to or at the beginning of a study introduces a variable which, although controlled, affects the magnitude of the results. To the extent that the diet is improved, the effects of the supplement are diminished. It appears that the national dietary in Great Britain was improved shortly before some studies were started there. About this change, authorities asserted that with provision of such foods as milk under the rationing system the British were better fed than ever. If such an improvement in diet occurred at a considerable period of time prior to or during the study, it would diminish the likelihood of marked effects from supplements within a short time. The effects of a change in diet during the course of a study, coupled with other circumstances calculated to minimize or obscure the results from supplements, are exemplified in the study reported by Fowke (1943). The experimental group receiving the multivitamin supplement showed no better growth or physical performance than the control group. But a survey at the beginning of the study and seven months later showed that meanwhile all diets had substantially bettered, partly from "general amelioration in the national food supply." Thus, the amount of potential improvement for both groups was decreased and the differential between them was narrowed. While the improvement in the diet was considerable, the potency of the vitamin supplement was low. In some instances the dietary change contributed to members of both groups greater amounts of a nutrient than did the supplement. In addition to the narrowing of the expected differences from dietary change and the low potency of the supplement, the sample was small. Under the circumstances, positive results would scarcely be anticipated.

Knowledge of basic diet, as well as of the initial nutritional status, permits a decision on what supplement is appropriate, whether it is likely to be effective and whether it is the best. Moreover, information about the diet indicates the variation that it is likely to introduce into the results and the magnitude of potential improvement. This information is helpful in deciding the size and composition of the sample. For example, it may be noted that in a study designed to ascertain whether a stock diet already amply demonstrated to be "adequate" could be

improved, as indicated by increased growth, extension of the period of full adult capacity and increased longevity, the sample was arranged to be larger than had usually been necessary in studies on animals with poor diets (Sherman and Campbell, 1928 and 1930).

Knowledge of the basic diet before as well as during the study and of any change in it helps in the analyses and interpretation of the results; indeed it may be the decisive point in reaching conclusions. For instance, the results in Fowke's study become understandable when it is noted that the basic diet improved greatly during the course of the study and that the dietary change contributed greater amounts of some nutrients than did the supplement (Fowke, 1943).

Report and description of information about the basic diet of each study permits not only analysis and interpretation of its results but comparison of dietary conditions in all studies, a step that is essential in comparison of their results. Unfortunately most reports on studies have not included the composition of the basic diet. From those few studies on man which have notes or comment on their basic diet, it would appear that the general dietary plane prior to the study was different for each. Also the dietary level during each study was dissimilar to that in others. These facts should be noted in resolving the seeming divergencies in their results.

4. Also to be considered are the environmental and endogenous conditions which operate to produce malnutrition by influencing the relation between supply and bodily requirements. Whereas supply is provided by food intake, the fundamental quantitative requirements for the various nutrients are determined by basal metabolic activity. Most simply, the relationship between supply and bodily requirements may be visualized as a ratio. When this ratio is favorable, when supply equals or exceeds requirements, the bodily processes operate toward good nutritional status. But when the ratio is adverse, when need exceeds supply, either by increase in the former or by decrease in the latter, the process which leads to the deficiency state is thrown into action.

A set of conditions, both external and internal, may affect supply or increase requirements above the basal level. Thus, they may influence both members of the ratio; some act on the numerator and others on the denominator. Examples of these conditions are growth, pregnancy, lactation, work, sunlight, climate, toxic materials and disease. These conditions undergo changes which modify the ratio. Most often several conditions are operating in combination, though not necessarily with equal potency. One may be dominant. One or more conditions may bring about increased requirements, and if these are not met by supply an adverse ratio results. Conversely, removal of the condition exercising critical or determinative influence halts the deficiency process or allows it to subside. Thus, in affecting the ratio these conditions act unfavorably or favorably on a person's nutrition.

In affecting the nutrition of a group of persons in a study, the condition may act on a few or on all persons in either group or in both. Their operation under some of these circumstances leads to variation in the results, introduces bias or affects the magnitudes of difference between the groups. Such operation, amounting to uncontrolled change in the conditions of a study, affects its results. Therefore, these conditions have an influence either favorable or unfavorable not only on nutrition but on the course and outcome of a study. But the direction of their effect is not necessarily the same on one as on the other. They may operate adversely on the outcome of the study by producing either a beneficial or a detrimental effect or by preventing a beneficial effect on nutrition. Likewise, they may operate favorably on the outcome by either an advantageous or a deleterious effect on nutrition.

Conditions may have an unfavorable effect on the outcome of the study through increasing variation without introducing bias or greatly changing the average results. If the difference between two groups is small, this increased variation may obscure its significance. But this effect is less important than that of bias.

In their unfavorable effects on nutrition, conditions may through bias act adversely on the outcome of a study. During the course of a study on the effect of a supplement on growth or physical performance, an epidemic may occur which, depending on its intensity, distribution and duration, may profoundly affect the results. It may occur predominantly in the control or in the supplement group or in both. If it occurs mainly in the control group, the difference between the two groups would tend to become magnified; if largely in the group given the supplement, the difference would be minimized. The former situation may explain the outcome of a study (Harper and others, 1943) in which subjects receiving a vitamin supplement showed a significant change in two physical tests, and a part of them in two additional tests. The sample was small; the initial statuses of the subjects were not detailed; the supplement contained only

vitamins A, C and D, and it was dispensed for only ten to eleven weeks. None of these circumstances was conducive to positive results, yet there were results. They are perhaps best explained by the authors. The control group suffered a 50 per cent greater incidence of minor respiratory and gastrointestinal ailments, which may have brought out the difference in performance. Here conditioning factors exerted their influence; despite the small sample, results were obtained.

If the epidemic occurs in both groups, it may still create a bias which decreases the difference between them. Apart from its direct deleterious effect on the nutrition of both groups, if it interrupts or stops the taking of the supplement, sickness will exert a greater influence indirectly on the group regularly given the supplement. This failure to take the supplement will tend to diminish the effects in the supplemented group and any differences from the control group. For this reason, Orr (1928) and Leighton and Clark (1929) attempted to exclude this source of bias and negation by omitting children with records of serious illness or absence of more than 25 per cent of the time.

Certain conditions may exert a favorable effect on nutrition but by creating a bias may have an unfavorable influence on the results of the study. Cessation of a condition of stress, such as increased sleep or diminished physical labor, may act mainly in the control group and diminish the difference in results between the two groups. It is misleading when such a condition operates only in the group given the supplement, for whether it or the supplement is responsible for any improvement cannot be decided and unwarranted credit may innocently but mistakenly be attributed to the supplement. This possibility was suspected in one study, and the results were held under advisement until subsequent data showed that it had not been a complication. In the report of the second study by the Department of Health for Scotland (Leighton and McKinlay, 1930) on the effects of feeding a supplement, the prefatory note gives the following reason for the repetition: "This previous test was open to the criticism that the striking improvement in the nutrition of the children who received the additional ration of milk was due not to the milk alone but in some measure to improved home conditions—food, sleep, and regulation of life—which might follow from the close surveillance which was kept over the children under test."

By bringing out difference between two groups without bias, conditions which have an unfavorable effect on nutrition may have a favorable effect on the outcome of a study. Thus there may be unusual or extreme conditions of inordinate intensity capable of bringing out differences in the subjects' nutritional status and functional performance. Conditions which place subjects under stress may be the decisive factor in intensifying differences in nutritional status and in revealing the deleterious effects of inferior status on health and performance. As a source of stress they may bring out differences not easily demonstrable otherwise. For such purposes they may be highly useful. For example, when resistance, not growth, is the objective of a study, the incidence of an epidemic at the proper time may provide the setting for studying the difference between groups. When nutritional status and diet are poor and an added condition, such as pregnancy, is in operation, the benefits from dietary supplementation may be striking.[5] When nutritional status and diet are at least fair or good, slight beneficial effects from an appropriate supplement may be expected to emerge within a limited time only under intense conditions of stress. All conditions are not equally exacting. Heavy work is forcible in the impact of its demands; it is likely to bring out inferiority in status or diet, as well as the beneficial effects of a supplement. In a recent study a conditioning factor actually was prominently and decisively in operation. When men were subjected to a severe test which involved both physical effort and coordination and brought them to a point just short of distress, addition of nicotinamide alone or with other vitamins previous to the test resulted in increased efficiency in performance of it (Frankau, 1943).

Unless these conditions with their influence on the outcome are properly appreciated, they may be a source of error in nutrition studies. If their presence or their change before or during the experimental period is overlooked, disregarded or uncontrolled or if their connection with nutrition is misunderstood, the results may be misinterpreted. Rightly comprehended and utilized, they may be of inestimable advantage.

5. For studying the possible effect of improvement in nutritional status from a supplement on such bodily functions as growth, physical performance and reaction to infection, it is necessary to select indexes and methods for appraising them. They should permit not only the initial and final status of the subjects in respect to these attributes to be ascertained and changes to be followed, but also differences be-

5. Ebbs and others, 1941 and 1942; Report of People's League of Health, 1942.

tween the two groups that may develop during the course of the study to be revealed. Since evaluation and expression of status in absolute terms are helpful, the judicious use of standards is sometimes necessary.

The effect of a supplement on bodily growth per se may be studied, apart from its use as an index of nutritional status. This is a study of the effect on physique. The measurements of the body used to ascertain or follow growth when it is taken as an index of nutritional status are equally applicable here. In all studies on the effect of a supplement on growth in human beings, data on body weight were recorded; in some weight was the only measure used. But weight is neither a sufficiently restrictive nor a detailed indicator of growth of physique. To obtain a more complete indication of the changes in growth, measurement of height also is to be recommended. Body length was measured in many studies; its measurement should be included in all studies. Depending on the nature of the study of the effects on growth, inclusion of additional bodily dimensions may also be desirable.

Unfortunately, among the indexes and tests of physical performance it is not known whether maximum output, rate of maximum output, endurance, rapidity or precision is the first or most easily affected with lowering of nutritional status. In short, it is not known which of these attributes of performance, if any, is the most sensitive to nutritional status. In induced acute deficiency states, it has been reported that there was lowered performance of tests that were not unusually severe. When nutritional status was not severely impaired, however, the difference in physical performance between the group given a supplement and the control group emerged in a test that was exhausting. The better the status, the more critical should be the test of physical performance. From the explanation of the operation of conditioning factors it is clear that the test should be sufficiently exhausting to put the subjects under stress or otherwise decisive. Hence, a test should be selected in relation to such terms of the study as its duration and the initial status of the subjects.

At the outset, in considering reaction to disease in relation to nutrition, it is to be noted that a distinction should be drawn between immunity and resistance. If the extent to which nutrition is improved does not confer increased immunity, it may impart increased resistance which is measurable in terms of lessened severity or duration of the disease. Furthermore, natural should be differentiated from acquired immunity.

Before selection of indexes for immunity and resistance, it is advisable to consider the characteristics of the specific disease or diseases which may be chosen to put these bodily reactions to test. The biology of the disease should be known and appropriate to the terms of the study, and vice versa. Whether a disease is acute or chronic, mild or severe, endemic or epidemic and high or low in incidence is important in deciding whether it should be selected for study in a particular sample of the population and in reaching a provisional estimate about the size of the sample and the duration of the study. In considering the study of several specific diseases of different characteristics, the terms of the plan should be sufficiently comprehensive to cover all of them.

With the recognition that these characteristics underlie plans for study of the relation of nutrition to immunity and resistance, it is clear that they also foreshadow and accentuate the difficulties attending it. A study of the reaction of the animal body to an experimentally induced infection presents no extraordinary difficulties. But a study of the reaction of a particular sample of the population during a definite period to the natural occurrence of a specific disease is filled with many contingencies. Nothing contains more elements of chance; the course of events is so fortuitous for such testing. A series of circumstances and conditions must be just right if conclusive results are to be obtained. They can be unpropitious in so many ways. This makes it difficult to formulate the details of a study to allow for every unforeseen contingency.

The characteristics of disease suggest the several ways that it may defeat the best laid plan and study. Whereas, in general, in occurrence and behavior, chronic disease is more apt to conform to a reasonably definite and stable epidemiologic pattern, an acute infectious disease is more apt to be a totally unpredictable phenomenon for precise planned study. First, it may not occur during the course of the study. Secondly, it may occur in too few cases. In either event, the incidence during the study would be so low that any effects of a supplement could not become demonstrable. Thirdly, it may occur too soon, too early in the course of the study. Here acute infections that appear in epidemic form are particularly troublesome. Their unpredictable occurrence introduces difficulties. Time is needed for development and increase of natural immunity against them; an ample period of supplementation must elapse in advance of the outbreak. If an epidemic must occur, there is a preferable time for it, namely, after

an extended period of supplementation. But such an outbreak cannot be scheduled. If it occurs too early, any effects of supplementation would not have had time to become effective. Indeed, premature occurrence would have an even more unfortunate effect of completely marring results. Fourthly, even if disease appears at an opportune time for study it may through excessive exposure and high virulence attack a large proportion, if not almost all, of the sample with considerable severity. Its overwhelming nature with high incidence may not permit relative individual resistances to it to be revealed.

The morbidity rate of a specific disease is an index of immunity to it. This rate may be determined by active steps in systematic and comprehensive case detection, whether by history, physician's diagnosis or verification of that diagnosis. In any event, the standards of diagnosis must be outlined. Or the incidence may be ascertained from absenteeism ascribable specifically to the disease under study. The severity and length of the specific disease may be an index of resistance to it. Graduation of the diseases into degrees of severity, in which complications and sequelae are also included, is one method of measuring that resistance. The period of confinement to bed, the period of invalidism, or of absenteeism from daily duties are also means of measuring resistance.

Instead of specific diseases, the incidence of any and all diseases as they occur may be the index of immunity or resistance. As previously mentioned, the cases may be systematically detected. But, owing to differences in diseases, they must be appropriately classified into groups. The greater the number of groups, the more likelihood of small numbers in each group, perhaps too small for statistical treatment. In lieu of active case detection for morbidity rate, records of absenteeism may be used in plants or schools. But when absenteeism is taken as the measure of sickness rate, it should be borne in mind that factors other than sickness are responsible for part of it. If there is an attempt to ascertain how much is due to sickness, a great strain is placed on the reliability and integrity of the absentee's explanation.

Properly selected indexes and methods for measuring growth, physical performance, immunity and resistance to disease should allow any differences that develop between the group given a supplement and the control group to be revealed. Furthermore, by comparing the data from physical measurements and tests with standards, it is useful to express initial status in absolute terms. Admittedly, the standards are not satisfactory. Nevertheless, a rough gradation and approximate rating, employed reservedly, give some indication of initial status of physique and physical performance. It is also useful to consider the initial status of the subjects in growth and physical performance in relative terms by comparing the initial data with those of other studies. The status of persons in respect to immunity and resistance to disease at the beginning of a study is not so easily ascertainable and is even less precise than the ratings for growth and physical performance. Yet even a rough estimate of the status of their reaction to disease has value for planning a study.

6. The initial status of the subjects with respect to growth, physical performance, immunity and resistance to disease, reflecting the magnitude of potential change, affects the outcome of the study and its interpretation. If height and weight are far below the expected average for age, there is greater possibility for increases in these measurements due to supplements. If, on the other hand, those measurements are already near the maximum at the beginning of the study, any increase in them from supplementation would be expected to be slight. It has already been cited that heights and weights for age have been increasing with each successive decade, and when a series of studies on supplements are arranged in chronologic sequence the initial measurements fall into an ascending sequence. It should also be reiterated that growth is not solely under the influence of diet. Also, if the measurements do not increase under supplementation, it does not necessarily mean that physique was already maximum.

The same considerations are applicable to the initial physical performance of the subjects. It has been reported that induced acute deficiency states brought about lowered performance while subsequent restoration of nutritional status led to recovery in output.[6] In short term experiments on small samples of persons of unknown initial nutritional status but certainly with no severe acute deficiency states, no superior physical performance developed in the experimental over the control group, as judged by tests that did not press the subjects.[7] But in a later study, roughly comparable to the preceding one in length and probably in initial nutritional status of the persons, difference in performance did develop between the two groups, as shown by

6. Egaña and others, 1942; Johnson and others, 1942; Barborka, Foltz and Ivy, 1943.

7. Foltz, Ivy and Barborka, 1942; Keys and Henschel, 1942.

a test that brought the subjects to the point of exhaustion (Frankau, 1943). Thus, when persons manifest only substandard nutritional status with somewhat lowered performance, a critical test is necessary to reveal the beneficial effects of a supplement administered for only a short time; a large sample and longer time would probably be required to allow the moderate amount of potential improvement from the supplement to be consummated and demonstrated if a less exacting test is used. Furthermore, the subjects may show considerable individual variation in their initial performance because of differences in motivation and training, and groups may exhibit marked differences in these respects. These two influences may be responsible for considerable change and variability in the results.

The initial status of subjects in immunity and resistance to disease is not easily ascertained, and data on it are not easily interpreted. Both acute infectious and contagious diseases present a particularly difficult problem. If the prevalence or incidence rate of them in the period just preceding the study has been high among the sample or the population from which it is drawn, it would seem that there is a greater possibility to demonstrate substantial improvement. But the affected persons may have acquired temporary or permanent immunity to the disease, depending on its nature, while the unaffected may have greater natural immunity or have been less exposed. Conversely, if the prevalence or incidence rate has been low, it might seem that further lowering could be only slight. But the low rate may have been due either to a high degree of immunity or to little exposure. These factors would enter into the outcome of the study. But such data are not easily analyzed, and they do not furnish a ready and certain guide for planning. Nevertheless, they give an insight into the composition of the sample. Chronic infectious diseases, with their steadier rate and lower grade, or minor infectious diseases, with their lower and shorter acquired immunity, if any, and their tendency to recurrence, present fewer of these complexities.

Since the initial status of the subjects with respect to growth, physical performance, immunity and resistance to disease has a bearing on the outcome of a study on the effects of a supplement, data on it are useful in laying plans for a study. This information permits variation within the sample to be ascertained, the appropriate size of the sample to be estimated, the sample to be tested and adjusted, if necessary, to exclude bias and adequate duration of the study to be scheduled. Furthermore, it permits comparison of different studies on this score. And it aids in analyzing and interpreting the results of each study and any difference in the results of several studies.

7. In the study of the relationship of nutrition to physique, performance and health, it is common to select a particular universe which is inferior in these respects and in which improvement might be most strikingly produced and demonstrated. But since it is equally desirable to learn whether an ordinary population, presumably only slightly below par, can be improved, such a universe may also be selected for study. Furthermore, there are other populations representing intermediate levels. Clearly these are all different universes.

When the universes are different, the conclusions drawn concerning one do not necessarily apply to another or to all others. Such a procedure leads to unwarranted generalization. Furthermore, when studies are drawn from different universes, comparison of their results must take that difference into account. For example, the physical measurements of the subjects recorded in Mann's report (1926) were initially inferior to those set forth in reports from subsequent studies. That difference should be borne in mind in considering why Mann's subjects showed benefits from milk supplements, although the sample was small.

It is obvious that the nature of the universe of a study must be known if its results are to be properly interpreted. Moreover, the sample drawn from the universe must be typical and representative of it. For these reasons the character of the sample should be carefully and adequately described. The members of the sample will differ in their nutritional status, height and weight, sickness record and physical performance; consequently, there will be variability in these items within the sample. In the division of the sample into experimental and control groups, it is necessary to have adequate data on its composition with respect to these items in order to demonstrate equality of distribution. It should be mentioned that for nearly every sex-age group in the Leighton and McKinlay study (1930) the controls in the beginning were consistently and significantly taller and heavier than the group given the supplement. An inescapable conclusion is that inadvertently some bias occurred. Part of the difference in results between the two groups in that study, pointing to favorable action of the food supplement, may have been due to this bias. If an epidemic supervenes in one group early in a study, at the least it opens the initial comparability of the groups in the sample to question and makes

subsequent comparison of doubtful value. Not unlikely its inopportuneness nullifies the study of any effect of improvement in nutrition on immunity and resistance to disease; and its occurrence at any time in the study may even have deleterious effects on the records of growth and physical performance.

8. Not to be overlooked in the interpretation and evaluation of results is the size of the sample. Its size must be considered in relation to the variability of the bodily functions selected as the indicators of effect (in these studies they are growth, physical performance, immunity and resistance); the magnitude of potential increase in these functions; the force of the substance being tested for its influence, and the period of its operation. Information on these points is revealed through environmental and endogenous conditions, the basic diet, the initial status of the subjects, the nature and potency of the supplement and the duration of the study.

Even in the most homogeneous group there is considerable variability in growth, arising mainly from environmental and endogenous conditions as well as diet. Hence, any modification of the growth pattern in the group must be of sufficient magnitude that the average change exceeds that which might be expected to occur under chance or sampling conditions. For instance, if the growth record of the group has potentiality for marked increase and if the stimulating force under test is strong and is applied for sufficient time, modification may become evident even though the sample is small. Thus, when the difference in growth between the experimental and the control group can be great or when the study is continued for a sufficiently long period for a slowly accumulating difference to become significant, a small sample may be satisfactory. But if the potentiality for increased growth is small or the test stimulus is weak or is applied for a limited period, the sample must be large. Hence, when the difference in growth between the experimental and the control group cannot or will not be great and the period of study is short, a large sample is needed if the results are to prove significant.

In the Leighton and McKinlay study (1930), in which the duration was short and the differences in results between the control and the experimental group were exceedingly small, an extremely large sample, 20,000 children, permitted these differences to be demonstrated as significant. Assuming the same magnitude of differences, if a much smaller sample had been taken, many of the differences would not have been significant. Conversely, the nonsignificance of the data on growth from children does not mean that comparable data from a larger sample might not be significant.

Just as in growth, so in performance of physical tests, a group of subjects show considerable variability. In addition to other conditioning factors, motivation and training are responsible not only for part of the variability but for fluctuations and trends over a period of time. Hence the effects of a supplement must be of considerable magnitude in order to become predominant and manifest. When the performance of interested, trained subjects is nearly standard, the amount of potential improvement is slight. For demonstration of it, a sample of sufficient size is one requisite.

Several studies on the effect of a multivitamin supplement on physical performance were conducted on small samples and for short periods. Indeed, the samples were extremely small and the duration extremely short. Even under these conditions severe physical stress on young men subsisting on an ordinary diet with no frank signs of an acute deficiency state brought out the benefits in physical performance from a vitamin supplement (Frankau, 1943). When the nutritional status of the subjects was appreciably lowered by an inadequate diet, their performance deteriorated; then with provision of a fortified diet or a multivitamin supplement, it improved.[8] But when small samples of subjects presumably with no marked impairment initially in nutritional status subsisted on an ordinary diet with multivitamin supplements for a short period, no increase in performance was observed.[9] Because the terms of the latter studies were restricted in so many respects, it is questionable that enlargement of the sample alone, unless to very great size, would have revealed significant increase in performance. It would likewise be a mistake to generalize from these results that multivitamin supplements are ineffective in increasing physical performance in such a population.

Almost the same principles and line of reasoning may be applied to the interpretation of results on the relation of nutritional status or vitamin supplementation to immunity and resistance. Evidence from numerous studies with animals indicates that immunity and resistance are seriously impaired when acute deficiency states are induced but are restored when the deficiency states are treated. But that multivitamin supplements will increase immunity and resistance in persons with no marked nutritional

8. Egaña and others, 1942; Johnson and others, 1942; Barborka, Foltz and Ivy, 1943.

9. Foltz, Ivy and Barborka, 1942; Keys and Henschel, 1942.

impairment cannot be said to be established, although there are considerable data pointing in that direction. It should be noted that if the incidence rate of a disease is low among subjects during the study, with exposure and virulence remaining constant, any demonstrable increase in immunity and resistance will not be great. Whether in short experiments under such conditions an extremely large sample would validate otherwise slight nonsignificant changes cannot now be said. As already discussed, other terms of the study weigh heavily in the determination and interpretation of results on immunity and resistance.

9. The nature and potency of the supplements bear on the results. With other conditions favorable, whether the supplement can be effective in increasing growth and improving physical performance and health will depend on whether it is appropriate. Not only in planning the study but in interpreting the results, it is therefore highly desirable to know the appropriateness of the supplement. For example, if the deficiency is only in calories, protein or minerals, an unlikely situation, a multivitamin supplement would not achieve the desired effect; supplying the missing nutrients would bring more effective results. If, however, the deficiency is in vitamins, they alone will produce maximum response. If the supplement does not supply all the nutrients in which the body or diet is deficient, the maximum response of the body will not be obtained and the effects of the supplement will be minimized. To insure use of the proper or most effective supplement, it is necessary to know what nutrients are needed and their level, as indicated by the initial nutritional status and the composition of the basal diet.

Often what starts out to be a study of the effect of improving nutrition on growth, physical performance, immunity and resistance to disease becomes a test of effectiveness of the supplement. This is particularly true if the results are negative. The effectiveness of the supplement is indissociably linked with the success of the study, generalizations about the supplement are drawn, and an absolute value is assigned to it. Often the verdict is unwarranted. When the results are negative, the supplement is labeled ineffective without examination of the role of the other conditions which have actually been the determining factors. Thereby erroneous beliefs, opinions and convictions arise.

It has generally been regarded that as a supplement a natural food is more apt to be effective than is a multivitamin-mineral preparation, is therefore more reliable and should be used in preference to it, particularly when the nutritional status of the subjects and the quality of their diet are unknown. The extreme of this view is that a vitamin-mineral supplement is likely to be ineffective. When a vitamin supplement seemingly has not produced results, it is usually suggested that a natural food supplement might have succeeded. It is a prevalent view that a natural food is superior and preferable to a multivitamin-mineral preparation as a supplement. Such opinions are based on the following arguments: A natural food is nutritively more complete than a vitamin-mineral preparation; a diet of natural foods supports nutrition in the rat more effectively than does a diet of individual known essential nutrients; many studies with children have indicated that a natural food supplement, such as milk, produced effects on growth; there is as yet little evidence with children to indicate that a vitamin-mineral supplement is similarly effective. But these arguments have serious flaws. It is advisable, therefore, to consider the issues in detail.

It is asserted that a natural food, since it contains more nutrients including unknown essentials, is more complete and adequate than a vitamin-mineral preparation. Inasmuch as deficiencies in the national diet are apt to be multiple, the most complete food is the best supplement. But obviously "natural food" is a much too general term for categorical statements. Specific foods differ in their content of nutritive substances and therefore their biologic value. No single foodstuff is independently adequate. Although most foods contain several nutrients, they have their deficiencies. A few ordinary foods are good or fair sources of two or more vitamins as well as of calories, protein and minerals; many foods supply fewer nutrients in moderate or high amounts. Hence, most individual foods have their inadequacies. Here it is necessary to draw a distinction between adequacy as the sole or principal source of nutrients in a diet and adequacy for purposes of supplementation. A food may be inadequate for the former but adequate for the latter. It is equally true that some foods might be so inadequate in numerous nutrients that as a supplement they would be inappropriate in most instances and would be applicable only in limited or in special circumstances. Since deficiencies in the national diet are multiple and those of vitamins and calcium are most common, many inadequate foods would not be satisfactory supplements. It is misleading, therefore, to generalize about the supplementary value of natural foods. A particular food must be specified and its adequacy as a supplement must be judged in reference to a particular diet and nutritional status.

In support of the superiority of natural food supplements, it is argued that a multivitamin-mineral preparation is incomplete; that it lacks certain essential nutrients, including some unknown vitamins, contained in natural foods. Because of its deficiencies, among which those of the unknown nutrients are regarded as most critical, it is assumed that a vitamin-mineral preparation is prevented from exerting its full effect as a supplement. Indeed it is believed that use of such a supplement would induce a deficiency state of unknown nature. Such an argument also explains the preference for a preparation of natural B complex over an aggregate of the major known B vitamins. Such a view ignores the function of a supplement, judges the vitamin addendum as though it were the sole or main source of all nutrients and applies to it the same criteria of adequacy as for the basic diet. Contrary to these points, it should be noted that, although a vitamin-mineral supplement does not provide protein, carbohydrate and fat, fewer diets are deficient in these nutrients than in vitamins and minerals. Admittedly, also, the usual vitamin-mineral supplement does not contain unknown or unidentified vitamins, and it may not contain newly identified vitamins. But it is not known how frequently the diet is deficient in them and whether the supplement should supply them, and it is yet to be demonstrated that absence of these substances from the supplement entirely or profoundly nullifies its effectiveness. More important, the major vitamins and calcium are the elements most commonly deficient in the national diet. It is true that growth is impaired by other deficiencies than vitamins; probably it is affected more promptly by lack of calories. But surveys show that usually vitamin and calcium deficiencies are the most prevalent and therefore the most likely dietary cause of impaired growth. A multivitamin-mineral supplement should supply those deficiencies. On an absolute basis it is nutritively incomplete; as a supplement it can be appropriate.

Evidence from experiments with rats is advanced to show the superiority of a natural food as a supplement. It is pointed out that better growth curves are obtained with a diet of natural foods containing as yet unidentified factors than with a "synthetic" diet containing a composite of individual nutrients, including vitamins. But here neither the natural foods nor the vitamin-mineral components are a supplement; they are an integral part of the respective basic diets. Hence the relative efficacy not of supplements but of basic diets is being compared.

As evidence of the inferiority of a vitamin-mineral preparation as a supplement, experiments with rats are cited in which pure vitamins and minerals are used in so-called "purified" diets to reveal new deficiency states. From lack of unidentified factors, such diets fail to support nutrition and lead to deficiency states. But the human diet is not the "purified" diet of the animal laboratory. It cannot be said that generally the human diet is greatly deficient in such unidentified factors. Furthermore, in the "purified" diet the vitamin-mineral components are the sole sources of specific nutrients, not supplements, whereas the issue is their efficacy as a supplement. Actually, from studies with rats there is good evidence attesting to the effectiveness of vitamin or mineral supplements, even singly, as a supplement. It is manifest from Sherman's studies [10] that provision of a single appropriate vitamin or mineral in generous amount as a supplement to a diet already good has definite beneficial results but that they are not demonstrable in a short period.

Several studies showing increased growth of children from a supplement of natural food form much of the support for its claims to superiority. But this generalization came largely from studies on one natural food. Milk, the natural food supplement most frequently used, contains most nutrients, has a good nutritive rating and would be expected to be effective as an accessory for the deficiencies in the ordinary diets of persons. But this expectation has not always been realized. In most studies it has been used successfully as a supplement,[11] yet in one (Wood and Simpson, 1937) its effect has been slight or erratic. In still another study (Chaney, 1923) it was reported that the effect of milk on the group under observation was surpassed by that of oranges. Wheat alone or in combination with yeast, while it has recognized deficiencies and would not be a complete or even effective supplement for all diets, has a fair biologic rating, which indicates that it might have supplemental value for many diets. In some instances it has been effective [12]; yet it has also been used without success (Ellis and Turner, 1936). It is evident that generalization on the merits of natural foods as a supplement based largely on

10. Sherman and Campbell, 1935; Ellis, Zmachinsky and Sherman, 1943.

11. Orr, 1928; Leighton and Clark, 1929; Leighton and McKinlay, 1930; Rabasse, 1932; Aykroyd, Krishnan and Madhava, 1937; Hunt, 1937; report of Milk Nutrition Committee, 1938.

12. Morgan and Barry, 1930; Summerfeldt and Ross, 1938.

studies of one food is overdrawn. Indeed, since natural food supplements, even those of high nutritive value, have not given uniform and consistent results, there is as yet no basis on this score for the doctrine of their superiority as supplements.

It should be borne in mind that other reasons besides appropriateness affect the results with supplements. It is informative to examine first the studies in which milk was an effective supplement as judged by increased growth of the subjects and to ascertain the reasons for the successful results. When the studies showing beneficial effects with milk as a natural food supplement are analyzed, it is found that they were conducted under one or more of the following conditions conducive to success: With increase in height and weight as the criterion of effect, the subjects selected were initially underweight and undersize; the sample from the population was large; the sample was rigidly selected to minimize the variability and lack of effect by excluding subjects with an inferior record of health and of school attendance; the supplement was given for a long period, a year at least. Thus a variety of conditions were responsible for the successful studies; each study was successful through a different favorable condition. From this analysis it is clear that even a highly nutritive food, such as milk, cannot be demonstrated to have supplemental action unless conditions are propitious. Whether a supplement will be judged to have been effective in improving nutritional status, growth, physical performance, immunity and resistance to disease will depend on all other conditions of the study.

As yet the evidence is scant that vitamin supplements increase growth in children. In some studies that have been conducted there was no apparent effect. Consequently this situation has given additional reason to view such supplements as inferior or even ineffective. But this view is not supported by firm, incontrovertible evidence; rather, it rests on lack of evidence and insufficient and invalid evidence. It has come about in part because there have been only a few studies on the subject, much fewer than studies on the supplementary value of milk. True, for the most part in these few studies, vitamin preparations as supplements have had no apparent effect on growth. But in instances of negative results, whether with a multivitamin or with a milk supplement, conditions adverse to the demonstration of positive effects other than the nature of the supplement were responsible for the outcome. None of the conditions just mentioned as favorable to the elucidation of positive effects from the supplement prevailed in the multivitamin studies. In fact, there is no study on growth in children with a multivitamin supplement which is entirely comparable to the successful studies with milk.

It is clear that in studies on supplementary values of foods and vitamin-mineral preparations and their effects in man there is too little evidence and some of it is misleading. Some of the unsatisfactory results issue from the inappropriateness of the supplement, but most of them from the unsuitable terms of the study. A natural food has never been compared with a vitamin-mineral supplement under the same conditions. But even if it were, the results might hold only for that condition. It cannot be generalized that as a supplement either a natural food or a vitamin-mineral preparation is superior. For a supplement should be appropriate to needs; and the nature of the deficiencies in the person and his basic diet determine those needs. For these reasons, in planning a study or in analyzing and interpreting its results, the nature and potency of the supplement are significant.

Finally, it is obvious that unless the subjects receive the supplement they cannot derive any benefit. To the extent that they do not receive it, they will derive lesser effects. When the supplement is distributed to groups in schools or factories, absenteeism, whether from sickness or from other causes, interrupts receipt of the supplement and diminishes the opportunity for it to be effective. For this reason Orr excluded from his results the data on children who had been absent for 25 per cent of the course of his study.

10. The influence of time has been mentioned previously in relation to almost every other condition. The length of a study determines the opportunity for operation of these conditions; hence the minimum duration for significant results is fixed by them. In the several studies in which milk as a supplement has brought improvement in growth, the length of the study varied from four months to three years. Mann (1926), reporting results on increased growth from supplementation during one to three years, asserted categorically: "No satisfactory deductions can be drawn from short periods of observation—such as three or six months." Under certain conditions his statement has validity; but although it directs much needed attention to an important consideration in studies, it is not valid as a generalization. The length of time necessary for demonstration of the effects of an appropriate and potent supplement depends on all of the previously mentioned conditions, but particularly

on initial status with potentiality for improvement and on the size of the sample.

In general, when growth is the index, the poorer the initial status, the smaller may be the sample or the shorter the time of the study. Conversely, the better the initial status, the larger the sample or the longer the time required for study. If the subjects' records are markedly inferior with respect to growth, improvement should be noted in less than a year in an adequate sample. Quite different is the situation in which nutritional status and previous diet are already fair or good. In contrast to the rapidity with which frankly poor rates of growth in rats can be increased—to reason in terms of experience with another species whose nutrition has been even more thoroughly studied—it may be seen in Sherman's studies on the effects of suitable supplements on animals with good growth on a good diet that the period is somewhat longer before a significantly increased rate is demonstrable. Then, too, improvement of "optimum" rate of growth in stock animals by modification of the stock diet has been gradual over the years.

In most of the studies on children in which milk as a supplement brought increase in the rate of growth within a few months, the initial status was inferior or a large sample was used. Studying a very small sample of children with a poor initial growth record, Mann (1926) recorded the effects of the milk supplement over a long period, one to three years. In another study (Bransby and others, 1944), in which the initial status and the basic diet of the subjects were better, the length of the study, nine months, may have been too short for the size of the sample to demonstrate improvement with respect to the particular criteria. Such an experimental period is comparable to ten or eleven days for rats. A small sample of rats already showing a satisfactory record of growth on a good diet would not be expected to increase their usual rate of growth to a demonstrable extent within ten or eleven days.

When persons manifest only somewhat lowered performance in physical tests, the amount of potential improvement is slight. Similarly, if immunity and resistance are near their maximum among the subjects, the possible change can be only small. Since substandard nutritional status is capable of improvement at various rates, depending on its character, any related increase in physical performance, natural immunity or resistance may be assumed to develop at a corresponding rate. In many, if not most, instances, considerable time may be necessary for first evidences of increase and still longer for full development of maximum physical performance and immunity. With a small sample and a slow and potentially slight increase in physical performance and immunity, it is logical to expect that a long period of supplementation will be necessary to bring out improvement.

In short term studies, induced impairment of nutritional status was accompanied by deterioration in physical performance and this was later improved by supplements, whereas subjects on an ordinary diet and presumably with no marked nutritional disturbance showed no increase in physical performance on receiving supplements for a similarly short period. Numerous experiments with animals have shown that severe deterioration in nutritional status is accompanied by rapid loss in immunity, which is quickly improved by provision of appropriate nutrients. As yet, no studies have been conducted on persons of substandard nutritional status, physical performance and immunity to ascertain whether provision of a vitamin supplement for a long period with improvement in nutritional status would confer increased physical performance and immunity. Although data from existing studies do not demonstrate the point, they do not disprove it. They are all of short term. The question remains open.

CONCLUSIONS

All of the ten conditions and terms discussed affect the course and outcome of a study. When precise information about some of them is lacking, that lack is often circumvented in the plan of the study by employment of a control along with the experimental group, an arrangement which allows the effects of the conditions to be equalized and canceled. It is reasoned that, all other conditions being equal, any effect of the supplement would become manifest. But mere equality of conditions does not insure applicable results. It is necessary to formulate certain conditions, such as the size of the sample and the length of the study, in the light of proximate knowledge of other conditions, so as to allow actual and full development of evidence. Otherwise, such a study gives limited and inadequate results liable to misinterpretation.

It is necessary to know and define the conditions and to interpret the results within their frame. For example, when a small sample of subjects manifesting no acute deficiency state or markedly impaired growth record and receiving an ordinary diet are provided with a vitamin supplement of definite nature and potency for a short period, they may show no increase in growth rate, physical performance and immunity

within that time. These results hold only for that particular ensemble of conditions. It would be unfortunate and unfounded to conclude from such results that nutrition, physical performance, natural immunity and health are not improved by supplements or that multiple vitamins are ineffective. Several changes in the conditions and terms of the study might have altered the results. Too often the limiting and specific frame of conditions is cast aside and the results are applied without restriction or are inserted into another frame. For each study on the effect of a supplement, the results must be interpreted and presented within the frame of the study, else they may lead to erroneous conclusions, even to sweeping and unwarranted generalization; and the results and conclusions of one study do not necessarily apply to a different setting.

Several studies, some pertaining to the effect of supplements on growth and others on physical performance, have yielded much variability in results. Some of the results have been in such seeming disagreement that conflict and confusion have ensued. It is to be noted that there are at least ten classes of conditions framing any study. Actually, the difficulty arising from variable and divergent results may be traced to dissimilarities in the conditions of the studies and failure to recognize them. So long as studies on the same topic are conducted under widely different conditions there will be different and contradictory results. Neglect or disregard for these conditions or failure to define or control them is likely to lead to results which may have limited scope, may be misunderstood and on comparison may appear confusing. The results of studies similar in their object should be compared in reference to their underlying conditions. Understanding of this fact is the first step in reducing the field to order. It is evident that results from studies in the same category but under dissimilar conditions should contribute not to identity but to unity. In attempting to compare, understand and unify results, it is necessary to recognize the dissimilar conditions. Then conflict and confusion give way to conformity and clarity.

Several studies have shown a beneficial effect of nutrition on growth and physical performance; the negative results in others are understandable for reasons herein set forth. To some persons it may appear that in the studies on "normal" subjects the benefits, while statistically significant, are not striking enough to be of practical value. But the same figures are averages containing a spread of results among which may well have been some of greater magnitude from individuals who were initially in poorer nutritive status and physical condition and who profited much more than the mean figure would indicate. Furthermore, in tests of supplements and nutritional status on growth, physical performance and immunity, distinction should be drawn between the early and the full effects. It is highly probable that all of the recorded positive results were early effects. Indeed, no studies on human beings have been conducted for a sufficient time to demonstrate the magnitude of improvement.

While this critique has been applied to studies on the effects of supplements, it is equally applicable to other types of study.

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INFECTIOUS DISEASES

TENTH ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS

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It is of interest to recall some of the advances made in the field of infectious diseases in the brief ten year period since these reviews have been prepared. Needless to say, the discovery and practical application of the sulfonamide compounds in 1935 and of penicillin in 1940 by European investigators were of epochal importance. The use of these substances has already caused a great reduction of the mortality rate and severity of diseases caused by pneumococci, hemolytic streptococci, staphylococci, meningococci and gonococci. So great is the value of these innovations that the use of other specific therapeutic agents for infections caused by some of these bacteria is nearly obsolete. Penicillin has the three properties of the ideal antiseptic which have long been sought without serious expectation of ever finding them combined in one substance, namely, enormous antiseptic power, almost complete indifference to the medium in which it acts and almost complete nontoxicity.

Great progress in the knowledge of the mild infections of the respiratory tract has been made beginning with the discovery of the cause of influenza in 1933. Pneumonias of nonbacterial or viral origin have come into prominence, and this has provoked the discovery of numerous causative micro-organisms and viruses. The same is true for encephalitis. Interest in the syndrome stimulated by the discovery of the cause of St. Louis encephalitis, which also occurred in 1933, led to the subsequent discovery of the viruses of equine encephalitis, spring-summer encephalitis and others. The discovery of jungle yellow fever and of an effective vaccine against yellow fever took place. The untoward development of jaundice among military personnel who received certain lots of the vaccine led to intensive research on various forms of acute hepatitis of unknown cause. Several other "new" diseases have been discovered, including Q fever, Bullis fever, ornithosis, acute infectious lymphocytosis and West Nile and Bwamba fevers, and several known infections have greatly increased in importance, such as coccidioidomycosis, toxoplasmosis and histoplasmosis. The relationship of worldwide rickettsial infections has been clarified. Other important contributions are the grouping and typing of hemolytic streptococci and the application of this knowledge in epidemiology; the extended use of the complement fixation reaction for the diagnosis of many infectious diseases; the deflation of the importance of focal infection, in its limited sense, to systemic diseases of unknown origin; the demonstration of the crystalline form of certain filtrable viruses, and the additional evidence of hereditary influences in tuberculosis and rheumatic fever.

In epidemiology much more attention has been directed to asymptomatic or mild grades of infection, which usually comprise the majority of attacks of many epidemic diseases in previously unrecognized or disregarded form. As examples coccidioidomycosis, malaria, yellow fever, infectious mononucleosis, viral pneumonia, poliomyelitis, mumps, trichinosis, bacillary dysentery and epidemic diarrhea may be cited. The mild forms in ambulatory patients are of great importance in the dissemination of some of these diseases. More significance is now attached to the importance of numerous infectious or contagious diseases of animals and birds in relation to man and their reciprocal transmission either directly or through the agency of insects. Among these diseases may be mentioned various forms of encephalitis, ornithosis, rickettsial diseases, kala-azar, the leptospiral diseases, the rat bite fevers, tularemia and brucellosis. Bacteria and viruses are now known to be unstable, changing frequently from one form or culture phase to another, to account for differences at times in their invasiveness, antigenicity and elusiveness to isolation, and to explain much previously obscure behavior. Methods better than the use of specific vaccines to control infections have been developed, particularly the sterilization of air by aerosols or ultraviolet rays to control air-borne infection and in the use of insecticides or repellents against insect-borne or arthropod-borne infections, especially typhus fever, malaria and yellow fever. The value of chemoprophylaxis with sulfonamide compounds and penicillin is under investigation.

Great advances in the knowledge of exotic diseases are being made incident to the worldwide dispersal of military forces, but much of the

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accrued information is no doubt still withheld for obvious reasons.

PENICILLIN

A report of a committee of the National Research Council [1] on the results obtained in 500 patients treated with penicillin confirmed the previous experience of British investigators. Penicillin, because of the limited amount available at the time, was used only for certain infections resistant to sulfonamide compounds. Later reports by various investigators published in symposiums in the March 4, 1944 issue of *The Journal of the American Medical Associaton* and in the April 15 issue of the *British Medical Journal* greatly amplify the information at hand as regards indications for the use of penicillin, its limitations, the dosage and methods of administration and its remarkable freedom from toxicity. Aside from slight differences of opinion as to dosage and route of injection, the conclusions of the various contributors are strikingly similar. In a directive issued by the War Production Board on May 1, 1944, when penicillin was released for limited civilian use, it is said to be the best therapeutic agent available for the treatment of: (*a*) staphylococcic infections, with and without bacteremia, (*b*) clostrial infections, (*c*) hemolytic streptococcic infections with bacteremia and serious local involvement, (*d*) anaerobic streptococcic infections, (*e*) pneumococcic infections and (*f*) gonococcic infections. Meningococcic infections are not mentioned, but it would seem that they should be included.

Penicillin is of probable value against syphilis, actinomycosis and bacterial endocarditis. It is of questionable value against mixed infections of the peritoneum and liver in which gram-negative bacteria are predominant. It is of no value and should not be used for any infections caused by filtrable viruses or by gram-negative bacilli (the typhoid-dysentery-colon group, Haemophilus influenzae, Bacillus proteus, Bacillus friedländeri, Bacillus pyocyaneus, Brucella melitensis and Pasteurella tularensis) or for histoplasmosis, acute rheumatic fever, diffuse lupus erythematosus, infectious mononucleosis, pemphigus, Hodgkin's disease, leukemia, ulcerative colitis, malaria, coccidioidomycosis, blastomycosis, moniliasis or cancer.

For Meningitis.—In the few reports thus far available on the treatment of human [2] and experimental [3] meningitis it is stated that intrathecal injection is necessary since penicillin does not readily diffuse into the spinal fluid. Cairns and his associates report recovery in 12 of 16 cases of pneumococcic meningitis. In my own experience [4] with several cases of pneumococcic and meningococcic meningitis and with 1 case of staphylococcic meningitis, recovery followed intravenous and intramuscular injection alone. If the infection involves meningeal tissues, why cannot penicillin reach it by way of the blood stream, and are bacteria in the spinal fluid of primary concern? Furthermore, penicillin injected parenterally does enter the spinal fluid.[4a]

For Syphilis.—Great interest is attached to this subject, and if the present favorable results are maintained the present mode of treating syphilis will be changed. Further observations over a period of years are necessary for complete appraisal of the value of penicillin in therapy. In the September 9 issue of *The Journal of the American Medical Association,* several authors report disappearance of the treponemes from the acute lesion, disappearance of early manifestations, reversal of the positive serologic reaction and improvement in late syphilis after the injection of penicillin. In experimental studies [5] on rabbits infected with Treponema pallidum, penicillin was active but only in relatively high concentration. Inadequate therapy led to development of resistance in the treponemes, which emphasizes the importance of early intensive therapy.

For Pneumonia.—Penicillin had no effect in 4 or 5 cases of "viral" pneumonia, and with the exception of one study [6] it was tested in cases of pneumococcic pneumonia only if the causative pneumococcus was resistant to sulfonamide compounds. In Tillett's series of 46 patients treated with penicillin alone, the substance was apparently equal to sulfadiazine in curative value.

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2. Cairns, H.; Duthie, E. S.; Lewin, W. S., and Smith, H. V.: Pneumococcal Meningitis Treated with Penicillin, Lancet **1**:655-659 (May 20) 1944.

3. Pilcher, C., and Meacham, W. F.: The Chemotherapy of Intracranial Infection, J. A. M. A. **123**: 330-332 (Oct. 9) 1943.

4. Price, A. H., and Hodges, J. H.: Treatment of Meningitis with Penicillin Injected Intravenously and Intramuscularly, New York State J. Med. **44**:2012-2014 (Sept. 15) 1944.

4a. Rosenberg, D. H., and Sylvester, J. C.: The Excretion of Penicillin in the Spinal Fluid in Meningitis, Science **100**:132-133 (Aug. 11) 1944.

5. Dunham, W. B.; Hamre, D. M.; McKee, C. M., and Rake, G.: Action of Penicillin and Other Antibiotics on Treponema Pallidum, Proc. Soc. Exper. Biol. & Med. **55**:158-160 (March) 1944.

6. Tillett, W. S.; Cambier, M. J., and McCormack, J. E.: The Treatment of Lobar Pneumonia and Pneumococcal Empyema with Penicillin, Bull. New York Acad. Med. **20**:142-178 (March) 1944.

Only 3 patients (6.5 per cent) died, and in these complications were present. The dosage is not yet standardized. It seems that in most cases 10,000 units given intramuscularly every three hours four times on each of three or four days suffices, but in some cases intravenous injections of 25,000 units were given in the first day. Now that physicians possess two powerful therapeutic agents for the treatment of pneumococcic pneumonia, the question arises, as in the case of meningococcic meningitis, whether or not serum therapy can be abandoned. It should be repeatedly reemphasized that, despite the availability of new therapeutic agents which attack pneumococci of all types, it is still necessary to make etiologic diagnoses by bacteriologic methods for the intelligent direction of therapy. The type of the infecting pneumococcus should be determined in every case.

Striking results were also obtained in the treatment of pneumococcic empyema with penicillin. In 6 of 7 patients recovery followed the intrapleural injection of penicillin without surgical intervention. I observed similar results in 5 cases by injecting from 20,000 to 30,000 units of penicillin into the infected cavity daily or on alternate days in from three to seven doses.

For Endocarditis.—Contrary to most reports of the ineffectiveness of penicillin in the treatment of subacute bacterial endocarditis is one report [7] in which success was claimed in several patients treated with heparin and penicillin combined. The same idea underlies this regimen as that proposed for combined therapy with heparin and a sulfonamide compound which has been given up as useless. Even if an attack can be successfully controlled, the nidus for future infections of the heart valve remains and the chances for reinfection will probably not be influenced by penicillin. Strains of nonhemolytic streptococci isolated from patients with subacute bacterial endocarditis are usually sensitive to penicillin in culture medium.[8]

The outlook for the treatment of acute ulcerative bacterial endocarditis with penicillin is more hopeful. Several instances of recovery have been reported from infections with hemolytic streptococci and pneumococci. I observed recovery of a patient with bacteremia, pericarditis and endocarditis resulting in mitral insufficiency from type XII pneumococci after pneumonia.

In experimental tuberculosis of guinea pigs,[8a] penicillin exhibited no effect. All preparations tested seemed to have some activity in reducing the extent of tubercle formation in infection of the chorioallantoic membrane of the developing chick, but without reducing the incidence of infection.

Penicillin had no effect on the course of rheumatic fever.[8b]

In Surgical Infection.—Lyons [9] reports on the use of penicillin for surgical infections. No opportunity occurred to test its use in treatment of clostridial infections, but the results in general are in keeping with those previously reported. Putrid infection of the wound was the most resistant complication encountered in treating gunshot wounds, but the use of penicillin permits active surgical intervention almost immediately and may reduce the incidence of this complication. According to experience in England,[10] penicillin is immensely superior to the sulfonamide compounds when applied locally. Meleney [10a] points out the precautions needed to evaluate penicillin therapy properly in the treatment of surgical infections.

Penicillin is reported to be successful in the control of a number of uncommon diseases experimentally established in animals,[11] namely, relapsing fever, psittacosis, ornithosis, leptospirosis, anthrax and rat bite fevers caused by Spiril-

7. Loewe, L.; Rosenblatt, P.; Greene, H. J., and Russell, M.: Combined Penicillin Heparin Therapy of Subacute Bacterial Endocarditis: Report of Seven Consecutive Successfully Treated Patients, J. A. M. A. **124**:144-149 (Jan. 15) 1944.

8. Dawson, M. H.; Hobby, G. L., and Lipman, M. O.: Penicillin Sensitivity of Strains of Non-Hemolytic Streptococci Isolated from Cases of Sub-Acute Bacterial Endocarditis, Proc. Soc. Exper. Biol. & Med. **56**:101-102 (June) 1944.

8a. Smith, M. I., and Emmart, E. W.: The Action of Penicillin Extracts in Experimental Tuberculosis, Pub. Health Rep. **59**:417-423 (March 31) 1944.

8b. Watson, R. F.; Rothbard, S., and Swift, H. F.: The Use of Penicillin in Rheumatic Fever, J. A. M. A. **126**:274-280 (Sept. 20) 1944. Foster, F. P.; McEachern, G. C.; Miller, J. H.; Ball, F. E.; Higby, C. S., and Warren, H. A.: The Treatment of Acute Rheumatic Fever with Penicillin, ibid. **126**:281-287 (Sept. 20) 1944.

9. Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army, J. A. M. A. **123**:1007-1018 (Dec. 18) 1943.

10. Penicillin in the Treatment of War Wounds, Foreign Letters, J. A. M. A. **125**:372 (June 3) 1944.

10a. Meleney, F. L.: Recent Experiences with Penicillin in the Treatment of Surgical Infections, Bull. New York Acad. Med. **20**:517-537 (Oct.) 1944.

11. Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimental Relapsing Fever, Proc. Staff Meet., Mayo Clin. **18**:457-467 (Dec. 1) 1943; Penicillin in the Treatment of Experimental Ornithosis, ibid. **19**:57-65 (Feb. 9) 1944; Penicillin in the Treatment of Experimental Leptospirosis Icterohaemorrhagica (Weil's Disease), ibid. **19**:89-99 (Feb. 23) 1944; Penicillin in the Treatment of Experimental Psittacosis, ibid. **19**:204-207 (April 19) 1944; Penicillin in the Treatment of Experimental Infections with Spirillum Minus and Streptobacillus Moniliformis (Rat-Bite Fever), ibid. **19**:257-264 (May 17) 1944; Penicillin in the Treatment of Experimental Infections with Bacillus Anthracis, ibid. **19**:492-496 (Oct. 4) 1944.

lum minus and Streptobacillus moniliformis. Relatively enormous amounts were needed to control infection with the Borelia of relapsing fever in rats and mice; hence, if the results can be translated to man, the use of penicillin for this disease does not seem warranted.[12] It inhibited the growth of typhus rickettsias in egg yolk sac cultures and reduced the mortality rate of experimentally infected mice.[13] Penicillin had no effect on infections with Trypanosoma lewisi[14] and Toxoplasma.[14]

Studies are in progress to devise methods of injection other than the ones now used so as to maintain a more constant amount of penicillin in the blood for a longer time. Thus far, promising results have been obtained by delaying the excretion of penicillin by the kidney, by delaying absorption by injecting it in a mixture of peanut oil and wax or by injecting it into locally refrigerated areas.

Intensive studies on the chemistry of penicillin are in progress. Penicillin has been demonstrated in crystalline form in its sodium salt, and attempts to synthesize it are under way.

In production of penicillin, unless care is taken cultures tend progressively to lose partly or wholly their ability to produce penicillin. The reason for this, according to Hansen and Snyder,[15] is that fungi, like bacteria, have variant forms, some of which do not form penicillin. With Penicillium notatum the C, or conidial, form gives rise to the M, or abnormal mycelial yellow pigmented, form in aging colonies. The types are physiologically and morphologically different. In mass transfer the M form is likely to become predominant. The C type, which makes penicillin, can be kept dominant by frequent transfer. A method is described by which a poor penicillin-producing culture can be rectified by eliminating the M form. In investigating maximum production of penicillin, the variant form which yields the best harvest should be selected and kept in its own culture phase.

It was known from earlier research that certain gram-negative bacilli make an enzyme which inhibits the bactericidal action of penicillin. Kirby[16] now reports the extraction of an inactivating substance from certain strains of coagulase-positive staphylococci which are naturally resistant to penicillin.

Other Antibiotic Agents.—Confusion has already arisen in the recognition and nomenclature of a number of antibiotic substances, as pointed out by Waksman.[17] For example, five preparations with different names, noncrystalline clavacin, claviformin, patulin, crystalline clavicin and clavatin, are identical, yet five different molds produce the substance. The matter is further complicated by the fact that a single mold may make several different antibiotic agents. Aspergillus fumigatus, for example, forms four.

Fumigacin (helvolic acid) and clavicin (patulin), derived from Aspergillus and Penicillium molds, are crystalline substances whose chemical nature has been determined. Clavacin in its present form is toxic, its activity is reduced by the presence of serum, and it kills leukocytes in weaker dilutions than those which inhibit bacterial growth. A curious example of difference of opinion developed in regard to the clinical use of patulin, a derivative of Penicillium patulinum,[18] in the treatment of the common cold. One group of British workers[19] after extensive study reported striking curative effects when the substance was inhaled, while other groups[20] obtained no effect whatever.

Waksman[21] reports the isolation of a new antibiotic agent, streptomycin, from the fungus Actinomyces griseus. The substance resembles streptothricin, previously studied by him, and

12. Eagle, H.; Magnuson, H. J., and Musselman, A. D.: The Therapeutic Efficacy of Penicillin in Relapsing Fever Infections in Mice and Rats, Pub. Health Rep. **59**:583-588 (May 5) 1944.

13. Greiff, D., and Pinkerton, H.: Inhibition of Growth of Typhus Rickettsia in the Yolk Sac by Penicillin, Proc. Soc. Exper. Biol. & Med. **55**:116-119 (Feb.) 1944. Moragues, V.; Pinkerton, H., and Greiff, D.: Therapeutic Effectiveness of Penicillin in Experimental Marine Typhus Infections in dba Mice, J. Exper. Med. **79**:431-437 (April) 1944.

14. Augustine, D. L.; Weinman, D., and McAllister, J.: Rapid Sterilizing Effect of Penicillin Sodium in Experimental Relapsing Fever Infections and Its Ineffectiveness in the Treatment of Trypanosomiasis (Trypanosoma Lewisi) and Toxoplasmosis, Science **99**:19-20 (Jan. 7) 1944.

15. Hansen, H. N., and Snyder, W. C.: Relation of Dual Phenomenon in Penicillium Notatum to Penicillin Production, Science **99**:264-265 (March 31) 1944.

16. Kirby, W. M. M.: Extraction of a Highly Potent Penicillin Inactivator from Penicillin Resistant Staphylococci, Science **99**:452-453 (June 2) 1944.

17. Waksman, S. A.: Purification and Antibacterial Activity of Fumigacin and Clavacin, Science **99**:220-221 (March 17) 1944.

18. Chain, E.; Florey, H. W., and Jennings, M. A.: Identity of Patulin and Claviformin, Lancet **1**:112-114 (Jan. 22) 1944.

19. Raistrick, H.: Patulin in the Common Cold: Collaborative Research on a Derivative of Penicillium Patulum Bainier, Lancet **2**:625-634 (Nov. 20) 1943.

20. Stuart Harris, C. H.; Francis, A. E., and Stansfeld, J. M.: Patulin in the Common Cold, Lancet **2**: 684 (Nov. 27) 1943. Patulin for the Common Cold, Foreign Letters, J. A. M. A. **126**:510 (Oct. 21) 1944.

21. Shatz, A.; Bugie, E., and Waksman, S. A.: Streptomycin, a Substance Exhibiting Antibiotic Activity Against Gram-Positive and Gram-Negative Bacteria, Proc. Soc. Exper. Biol. & Med. **55**:66-69 (Jan.) 1944.

like the latter substance is selective in its effect against gram-negative bacteria, including typhoid, dysentery and colon bacilli. The two substances may be related.

Tyrocidin [22] inhibited growth of Leishmania tropica, Trypanosoma cruzi and Trypanosoma lewisi but not of Leptospira icterohaemorrhagiae or of Bartonella bacilliformis. Tyrothricin killed Trichomonas vaginalis. In patients, tyrothricin caused initial disappearance of the organism but had no effect on relapses. Gramicidin had no effect on leptospiras or bartonellas, which are gram-negative organisms.

CHEMOTHERAPY WITH SULFONAMIDE COMPOUNDS

Interest in chemotherapy with sulfonamide compounds has been surpassed by that devoted to penicillin and other antibiotics. In the next few years the relative importance of these two great groups of substances in the treatment of various infections will be clarified. For certain infections penicillin no doubt will be the drug of choice. The sulfonamide compounds are still indiscriminately used and often wasted. It is said that 5,000 tons of sulfonamide compounds were manufactured in this country last year. This is enough to give every person in the United States about 30 Gm. during the year. For a critical discussion of the use of therapy with these drugs and of the difficulties which arise in evaluating the effects of the treatment, reference should be made to Meleney's paper.[23]

No new compounds superior to those available at present have been synthesized, and one wonders if much more can be expected along these lines unless some radically different combination is made.

Sulfamerazine, or sulfamethyldiazine (2-sulfanilamido-4-methyl-pyrimidine), is a new sulfonamide compound which was thought to have several advantages over sulfadiazine.[24] Since it appears quickly in large amounts in the blood and remains somewhat longer than sulfadiazine, somewhat smaller doses at longer intervals were therefore believed to be practical. However, this apparent advantage is offset by evidence that more of the drug than of sulfadiazine is bound to serum protein and thereby rendered inert.[25] Sulfamerazine is also somewhat more toxic. Sulfadiazine is still the drug of choice. Sulfadiazine is also superior to the less soluble compounds for treating certain infections of the intestine.

According to Norris,[26], sulfadiazine given orally eventually appears in the bronchial secretion of patients with bronchiectasis in amounts less than half of that in the blood. Chemotherapy combined with bronchoscopic drainage resulted in a reduction of the amount of sputum and altered the bacterial flora. Chemotherapy should be helpful if given before lobectomy and deserves a trial in nonsurgical cases of bronchiectasis.

Rather unexpected results were obtained by Nixon and his associates [27] in several cases of agranulocytosis resulting from sulfadiazine therapy. Instead of stopping the use of the drug when agranulocytosis was noted, they continued giving it, and with beneficial effect. Apparently spontaneous regeneration of polymorphonuclear leukocytes occurred during therapy even though the drug seemed to be the cause of the initial depression. Sulfadiazine, they state, may be valuable in combating the infection which usually accompanies agranulocytosis.

Several more cases of actinomycosis successfully treated with sulfonamide compounds are described,[28] but because of the chronicity of the disease patients should be observed for years before being reported as cured.[28a]

According to Spink and his co-workers,[29] strains of staphylococci resistant to sulfonamide

22. Weinman, D.: Effects of Gramicidin and Tyrocidine on Pathogenic Protozoa and a Spirochete, Proc. Soc. Exper. Biol. & Med. **54**:38-40 (Oct.) 1943.

23. Meleney, F. L.: The Difficulty of Evaluating Drug Treatment in Surgical Infections, J. A. M. A. **124**:1021-1026 (April 8) 1944.

24. Gefter, W. I.; Rose, S. B.; Domm, A. H., and Flippin, H. F.: Studies on 2-Sulfanilamido-4-Methyl-Pyrimidine (Sulfamerizine, Sulfamethyldiazine) in Man: III. The Treatment of Meningococcic Meningitis, Am. J. M. Sc. **206**:211-216 (Aug.) 1943. Flippin, H. F.; Gefter, W. I.; Domm, A. H., and Clark, J. H.: IV. The Treatment of Pneumococcic Pneumonia, ibid. **206**: 216-221 (Aug.) 1943. Hall, W. H., and Spink, W. W.: Sulfamerizine: Clinical Evaluation in One Hundred and Sixteen Cases, J. A. M. A. **123**:125-131 (Sept. 18) 1943. Hageman, P. V.; Harford, C. G.; Sobin, S. S., and Ahrens, R. E.: Sulfamerizine: A Clinical Study of Its Pharmacodynamics, Therapeutic Value and Toxicity, ibid. **123**:325-330 (Oct. 9) 1943.

25. Dowling, H. F.; Dumoff-Stanley, E.; Lepper, M. H., and Sweet, L. K.: Relative Toxicity of Sulfamerizine and Sulfadiazine, J. A. M. A. **125**:103-105 (May 13) 1944.

26. Norris, C. M.: Sulfonamides in Bronchial Secretion: The Effect of Sulfonamides in Bronchiectasis, J. A. M. A. **123**:667-670 (Nov. 13) 1943.

27. Nixon, N.; Eckert, J. F., and Holmes, K. B.: Treatment of Agranulocytosis with Sulfadiazine, Am. J. M. Sc. **206**:713-721 (Dec.) 1943.

28. Lyons, C.; Owen, C., and Ayers, W. B.: Sulfonamide Therapy in Actinomyotic Infections, Surgery **14**:99-104 (July) 1943. Ladd, W. E., and Bill, A. H.: Actinomycosis of Chest with Spread to Abdomen: Report of Case Cured with Sulfadiazine, New England J. Med. **229**:748-750 (Nov. 11) 1943.

28a. Benbow, E. P.; Smith, D. T., and Grimson, K. S.: Sulfonamide Therapy in Actinomycosis: Two Cases Caused by Aerobic Partially Acid Fast Actinomyces, Am. Rev. Tuberc. **49**:395-407 (May) 1944.

compounds are being encountered with increasing frequency, and the majority of such strains are obtained from patients who had had prior therapy with such compounds. Accordingly, a study was made to compare the resistance in culture mediums of many strains of staphylococci to the effects of penicillin and of sodium sulfathiazole. Of 68 strains, 12 per cent were resistant to amounts of penicillin effective in inhibiting most strains. Eighteen per cent were so sensitive that they failed to grow in the presence of 0.05 unit. About 28 per cent of the strains were highly resistant to sodium sulfathiazole. There was no relationship between resistance to penicillin and to the sulfonamide compound. Since some strains of staphylococci seem to be naturally resistant to penicillin and yet sensitive to sulfathiazole, it would seem that a combination of the two substances may be of advantage in treating certain serious infections.

With gonococci there is a correlation between the resistance to sulfonamide compounds in the test tube and in the body.[30] If the infecting gonococci are found to be resistant in culture mediums, chemotherapy will be ineffective and should not be used. As a rule sulfonamide compounds act promptly in gonorrhea or not at all, regardless of the duration of the disease.

The use of chemotherapy with sulfonamide compounds for other infections is discussed in appropriate places.

DISEASES CAUSED BY COCCI

Pneumonia.—"Lobar pneumonia as it was known a comparatively few years ago, no longer exists today" according to Plummer,[31] in whose experience the number of cases of pneumococcic pneumonia observed last winter was about one third of the number in a similar period ten years ago. The mortality rate has also been reduced from 30 per cent to about 10 per cent by chemotherapy with sulfonamide compounds. In another study,[32] the mortality rate was said to have been reduced from about 21 per cent to 4 per cent among industrial workers. The incidence of all forms of pneumonia increased slightly in the latter group, probably because of overwork (?) in wartime or of the increase in the number of cases of nonbacterial pneumonia.

Typical cases of pneumococcic pneumonia are indeed less often encountered than formerly, and in my experience the percentage of cases in which the pneumococci isolated from the sputum are "untypable" or pneumococci cannot be recovered at all has increased. Furthermore, during the past winter there were numerous patients with pneumonia clinically like the pneumococcic form from whom no pneumococci could be recovered and who failed to respond either to sulfadiazine or to penicillin but recovered anyway after seven to fourteen days. No careful studies have as yet been published about the apparent change in the character of the pneumonia in the current cases. There were fewer cases of the viral or nonbacterial forms in the winter of 1943-1944 than in 1942-1943. It is still not only desirable but necessary to determine the cause in every case of pneumonia, so as to avoid use of sulfonamide compounds if it is not indicated, to conserve the present limited supply of penicillin and to determine the place, if any, of serotherapy.

Pneumococci resistant to sulfonamide compounds are found in from 2 to 6 per cent of cases of pneumococcic pneumonia before treatment, and pneumococci occasionally become resistant in patients after brief or routine chemotherapy.[33] However, evidence is at hand that perhaps some degree of resistance of pneumococci to sulfonamide compounds develops regularly in all cases in which chemotherapy is prolonged. Pneumococci which acquire a high degree of resistance retain that resistance for an indefinite period.[34] Theoretically, therefore, the multiplication and dissemination of pneumococci resistant to sulfonamide compounds that are capable of causing pneumonia would create a serious hazard were it not for the availability of penicillin. One may also consider the possibility of the development of resistant pneumococci or other bacteria in patients who inadvisedly receive chemotherapy with sulfonamide compounds for minor infections of the respiratory tract or other infections.

In Harris' study [35] 38 per cent of patients who had had pneumococcic pneumonia and were

29. Spink, W. W.; Ferris, V., and Vivino, J. J.: Comparative in Vitro Resistance of Staphylococci to Penicillin and to Sodium Sulfathiazole, Proc. Soc. Exper. Biol. & Med. **55**:207-210 (March) 1944.

30. Goodale, W. T., and Schwab, L.: Factors in the Resistance of Gonorrhea to Sulfonamides, J. Clin. Investigation **23**:217-223 (March) 1944.

31. Plummer, N.: The Treatment of Lobar Pneumonia, Bull. New York Acad. Med. **20**:73-86 (Feb.) 1944.

32. Untergleider, H. E.; Steinhaus, H. W., and Gubner, R. S.: Public Health and Economic Aspects of Pneumonia: A Comparison with Pre-Sulfonamide Years, Am. J. Pub. Health **33**:1093-1102 (Sept.) 1943.

33. Hamburger, M.; Schmidt, L. H.; Sesler, C. L.; Ruegsegger, J. M., and Grupen, E. S.: The Occurrence of Sulfonamide-Resistant Pneumococci in Clinical Practice, J. Infect. Dis. **73**:12-30 (July-Aug.) 1943.

34. Sesler, C. L.; Schmidt, L. H., and Belden, J.: Studies on Sulfonamide-Resistant Organism: IV. Retention of Resistance by Pneumococci, Proc. Soc. Exper. Biol. & Med. **56**:42-45 (May) 1944.

35. Harris, W. H.: Relationship of Chemotherapy in Pneumonia to the Persistence of Pneumococci, Bull. Johns Hopkins Hosp. **72**:338-346 (June) 1943.

treated with sulfonamide compounds still carried the type of pneumococci responsible for their infection after recovery. Seven per cent carried pneumococci of another type. It is obvious that chemotherapy does not significantly reduce the convalescent carrier rate after pneumococcic pneumonia. Unfortunately, no mention is made as to whether or not the persisting pneumococci were resistant to sulfonamide compounds. In other studies,[33] pneumococci resistant to sulfonamide compounds were found to be present in the nose and throat four months after recovery from pneumonia.

The treatment of pneumococcic pneumonia with penicillin is discussed on page 281.

Blankenhorn and Grupen [36] report recovery of 8 patients with pneumococcic pyarthrosis after treatment with one of several sulfonamide compounds. Repeated aspiration, but not surgical drainage, was done in addition.

Eddy [37] proposes a scheme to lessen the confusion and simplify the classification of the great number of types of pneumococci now known to exist. Since several types have related subtypes to designate which letters have been affixed to numbers, for examples, IVA and VIIB, she prefers to discard the letters and to give every separate type only a number. This scheme brings the total number of types to about seventy-five. In another paper she proposes certain tentative groupings of types to simplify the manufacture and use of both diagnostic and therapeutic antiserums, since it is commercially unfeasible to keep a stock of seventy-five separate types of serum. One wonders whether much more work along these lines is warranted until the fate of therapeutic antipneumococcus serum is decided.

Under the electron microscope [38] the capsule of the pneumococcus looks like a gel closely applied to the bacterial cell wall. It swells about twenty-five fold under the influence of type-specific antiserum. Avery and his associates [39] report the discovery of an acid isolated from the pneumococcus which is apparently responsible for the transformation of a type IIR pneumococcus into type III.

Hemolytic Streptococcic Infection.—Opportunity was taken to study the epidemiology of hemolytic streptococcic infections in a carefully controlled group of children.[40] Among these children a given type of group A streptococci may become widely disseminated without causing any sickness. Infections of the respiratory tract were seldom caused by types of streptococci prevalent in the group but often followed the introduction of a different type. Major outbreaks were not usually preceded by a rise in the carrier rate among the residents. Contrary to general opinion, persons may become carriers of hemolytic streptococci without having become infected. About 30 per cent of "new" children admitted to the group were carriers of various types of group A streptococci, but with few exceptions these strains did not spread to others and vanished after a few months.

In children who had been sick, a type-specific immunity seemed to follow, since reinfection with the type which caused the preceding disease never occurred.[41] When repeated attacks of streptococcic infections did occur they were caused by streptococci of different types. In tests made on children involved in an outbreak of infection with type 36 streptococci, bacteriostatic properties were present in the serum afterward, but none was demonstrable in the blood of children who escaped infection and were presumably immune. Some other unknown factors evidently exist to provide specific immunity. If specific immunity could be developed it would no doubt be superior and preferable to chemoprophylaxis with sulfonamide compounds.

Other studies [42] also emphasize the variation in immunologic response of different persons to a given infection. After an epidemic of type 15 hemolytic streptococcic tonsillitis only 14 per

36. Blankenhorn, M. A., and Grupen, E.: The Treatment of Pneumococcic Pyarthrosis, J. A. M. A. **122**: 1177-1179 (Aug. 21) 1943.

37. Eddy, B. E.: Nomenclature of Pneumococcic Types, Pub. Health Rep. **59**:449-451 (April 7) 1944; A Study of Cross Reaction Among the Pneumococcic Types and Their Application to the Identification of Types, ibid. **59**:451-468 (April 7) 1944; Cross Reactions Between the Several Pneumococcic Types and Their Significance in the Preparation of Polyvalent Antiserum, ibid. **59**: 485-499 (April 14) 1944.

38. Mudd, S.; Heinmets, F., and Anderson, T. F.: The Pneumococcal Capsular Swelling Reaction, Studied with the Aid of the Electron Microscope, J. Exper. Med. **78**:327-332 (Nov.) 1943.

39. Avery, O. T.; MacLeod, C. M., and McCarty, M.: Studies in the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III, J. Exper. Med. **79**:137-158 (Feb.) 1944.

40. Kuttner, A. G., and Krumwiede, E.: Observation on the Epidemiology of Streptococcal Pharyngitis and the Relation of Streptococcal Carriers to the Occurrence of Outbreaks, J. Clin. Investigation **23**:139-150 (March) 1944.

41. Kuttner, A. G., and Lenert, T. F.: The Occurrence of Bacteriostatic Properties in the Blood of Patients After Recovery from Streptococcal Pharyngitis, J. Clin. Investigation **23**:151-161 (March) 1944.

42. Rantz, L. A.: Group A Hemolytic Streptococcic Antibodies: III. A Study of the Simultaneous Infection of a Large Number of Men by a Single Type, Arch. Int. Med. **73**:238-240 (March) 1944.

cent of patients acquired specific agglutinins. There was no correlation between the initial streptolysin titer and the rash; the rash toxin is distinct from the labile hemolysin.

Further epidemiologic studies were made by a commission on air-borne infections to determine the type of hemolytic streptococci most likely to cause scarlet fever.[43] Although all numbered types have been reported to cause the disease, at certain times certain types are particularly operative while at others the same types are innocuous. It may be that different strains of the same numbered type vary in their ability to make a rash toxin or that the same strain varies at different times. Both possibilities may exist. At one station hospital types 19, 1, 6 and 7 accounted for 53 and 67 per cent respectively of all types prevalent in successive seasons, yet type 3 caused scarlet fever in 47 per cent of patients it infected and type 17 in 32 per cent. Types 19 and 1 together caused the disease in only 17 per cent of patients and type 6 in none. The results resemble those of the report[40] previously discussed in that the types of hemolytic streptococci most prevalent do not necessarily cause infections and recently introduced different types often do.

Interesting studies were made in a food-borne outbreak of hemolytic streptococcic infection.[44] At a church fair, ham prepared by a person in the early stage of scarlet fever was apparently infected with type 2 streptococci. Of 182 persons who attended the fair, 102 who presumably ate ham, or 56 per cent, became sick. There were 24 persons with scarlet fever, 56 with sore throat, 7 with diarrhea and 4 with vomiting; 3 had nausea and 8 had miscellaneous complaints. Many who had scarlet fever also had gastroenteritis. Apparently both the erythrogenic and the enterotoxic toxins were operative to cause the variety of responses noted, the symptoms of one predominating in some patients and of the other in others.

Another epidemic of "septic" sore throat apparently had its source in dried milk contaminated in a mixing machine during preparation for use.[45]

A portion of a group of nurses who received immunizing doses of scarlet fever toxin had pains in various joints therefrom.[46] Investigation showed that sensitiveness to the toxin was present in a high proportion of those who had had rheumatic infection or who harbored chronic streptococcic infection (streptococcosis), and not in others.

Meningococcic Meningitis.—In 1943 meningococcic meningitis reached the highest incidence in the United States in thirty years, with nearly 18,000 reported cases.[47] The outbreak of epidemics in military posts stimulated considerable interest in the subject. Clinically no new facts emerged, but the effect of sulfonamide compounds in controlling the infection and in some instances in preventing it was striking. In one group of 80 patients with meningitis treated with sulfadiazine, only 1 died and all of 32 patients with meningococcemia alone recovered.[48] Penicillin is perhaps of equal value. With two specific agents now available, the need for antimeningococcus serum has all but disappeared, even though an improved serum prepared in rabbits is available.

Remarkable results also occur in ridding the nasopharynx of meningococci in carriers with small doses of sulfadiazine.[49] This effect led to a practical application of chemoprophylaxis by several observers. In one study, by giving sulfadiazine to 15,000 soldiers in doses of 2 to 3 Gm. for two to three days during an epidemic season the carrier rate was reduced from about 36 per cent to less than 5 per cent in the groups studied; at the same time the carrier rate among untreated soldiers increased to nearly 56 per cent. Meningitis did not develop in any of the treated group, while during the same three week period it occurred in 23 of 9,300 untreated soldiers. To be successful chemoprophylaxis must be applied only to well controlled groups of people, as in military establishments, boarding schools and resident institutions, where the whole group can

43. Hamburger, M.; Hilles, C. H.; Hamburger, V. G.; Johnson, M. A., and Wallin, J. G.: Ability of Different Types of Hemolytic Streptococci to Produce Scarlet Fever, J. A. M. A. **124**:564-566 (Feb. 26) 1944.

44. Getting, N. A.; Wheeler, P. M., and Foley, G. E.: A Food-Borne Streptococcus Outbreak, Am. J. Pub. Health **33**:1217-1223 (Oct.) 1943.

45. Allen, R. F., and Baer, L. S.: Outbreak of Septic Sore Throat Due to Reconstructed Powdered Milk, J. A. M. A. **124**:1191-1193 (April 22) 1944.

46. Rhoads, P. S., and Afremow, M. L.: Significance of Joint Pains Caused by Sterile Streptococcus Toxin, Ann. Int. Med. **19**:60-63 (July) 1943.

47. Meningococcus Meningitis in the United States During 1943, Pub. Health Rep. **59**:469-471 (April 7) 1944.

48. Daniels, W. B.; Solomon, S., and Jaquette, W. A.: Meningococcic Infection in Soldiers, J. A. M. A. **123**:1-9 (Sept. 4) 1943.

49. Mueller, J. H.: Relation of the Carrier Problem to Epidemic Meningitis, Ann. Int. Med. **18**:974-977 (June) 1943. Kuhns, D. M.; Nelson, C. T.; Feldman, H. A., and Kuhn, L. R.: The Prophylactic Value of Sulfadiazine in the Control of Meningococcic Meningitis, J. A. M. A. **123**:335-339 (Oct. 9) 1943. Lewis, W. B.; Bolker, H., and Klein, D.: Mass Treatment with Sulfadiazine: Its Effect During an Outbreak of Meningococcic Meningitis, Mil. Surgeon **93**:443-447 (Dec.) 1943.

be treated at once and closely observed and no carriers permitted to enter. Once chemoprophylaxis is discontinued, the carrier rate gradually increases during the subsequent weeks to its usual level. Except under unusual circumstances chemoprophylaxis is not recommended for the difficultly controlled civilian population. It seems better to treat the disease as it arises. Kuhns [50] describes practical methods for the detection of carriers and for the culture of meningococci.

The importance of making early diagnosis is obvious, especially in cases in which meningeal signs are absent. Several investigators [51] recall the value of making smears from the purpuric lesions of the skin. By the use of this technic early diagnosis was made in 80 per cent of cases, and in 4 cases it provided the only means for the etiologic diagnosis. In the examination of smears, extracellular bacteria must be regarded as possible contaminants; intracellular gram-negative cocci are highly suggestive, and positive cultures confirm the diagnosis.

The chick embryo serves as a good culture medium for the prompt identification of meningococci and other bacteria, especially when bacteria fail to grow on the usual agar mediums.[52] Diffuse daylight, even in winter and spring, is germicidal to meningococci.[53] If protected from light, meningococci are more resistant to dehydration than is generally supposed.

A case of meningitis caused by Neisseria perflava is reported in which sulfonamide compounds had no effect.[54]

DISEASES CAUSED BY BACILLI

Bacillary Dysentery.—Hardy and Watt [55] report an exhaustive study of acute diarrheal diseases, dealing chiefly with bacillary dysentery, amebic dysentery and the Salmonella infections of "food" poisoning. Surprisingly, no mention is made of the syndrome called "epidemic diarrhea, nausea and vomiting" discussed later in this review, which according to indications was more prevalent in this country in late 1943 than all other diarrheal diseases combined. Callender [55a] likewise fails to mention it in his review.

Several important points seldom emphasized are brought out: The carrier state for "para" dysentery bacilli (Flexner, Sonne, etc.) terminates in less than one year after recovery from the disease; chronic carriers, if there are any, are exceedingly rare. The great majority of persons with active infection are never recognized, because as a rule only the severely sick patients seek medical advice. For example, in one group studied only 2 patients were under medical care but 380 others, with mild or disregarded infection, had positive fecal cultures. It becomes clear, then, why epidemic diarrheal diseases are deceptively sporadic if only the severe forms are diagnosed. An attack of bacillary dysentery provides a certain degree of specific protection against subsequent attacks with the same variety of bacilli but not against infection with other varieties. The transmission of the infection seems more dependent on contact with persons who have symptomless infection than on infection through the medium of milk, water, food or insects. The authors are impressed with the wide variability of symptoms, from the great majority of asymptomatic forms and of "simple diarrhea" to the rare fulminating form. The word "shigellosis," comparable to "brucellosis," is suggested to name all infections, latent, mild or severe, caused by pathogenic varieties of Shigella. Etymologic purists may take offense at the fusion of Japanese and Greek elements.

In almost all the cases studied the disease terminated spontaneously within a week; in adults in from two to four days. This raises the important question as to the need of using sulfonamide compounds for so mild a disease. Perhaps some of the favorable reports concerning chemotherapy already published reflect this early spontaneous recovery, and besides one has to deal with the toxic effects of the drugs used as well. For example, although, Smith [56] reports favorable results in 44 cases, 21 of the patients acquired a rash due to the drug used, and in some cases the reaction to sensitization was severe. In Hardy and Watt's experience chemotherapeutic response was best in infection with the Flexner variety and least with Sonne

50. Kuhns, D. M., and Feldman, H. A.: Laboratory Methods Used in Determining the Value of Sulfadiazine as a Mass Prophylactic Against Meningococcic Infections, Am. J. Pub. Health **33**:1461-1465 (Dec.) 1943.

51. Tomkins, V. N.: The Diagnostic Value of Smears from Purpuric Lesions of the Skin in Meningococcic Disease, J. A. M. A. **123**:31 (Sept. 4) 1943. Bernhard, W. G., and Jordan, A. C.: Purpuric Lesions in Meningococcic Infections, J. Lab. & Clin. Med. **29**: 273-276 (March) 1944.

52. Blattner, R. J.; Heys, F. M., and Hartmann, A. F.: Advantages of Egg Culture Technic in Infectious Diseases, Arch. Path. **36**:262-267 (Sept.) 1943.

53. Miller, C. P., and Schad, D.: The Resistance of Meningococci to Drying, J. Bact. **47**:71-77 (Jan.) 1944; Germicidal Action of Daylight on Meningococci in the Dried State, ibid. **47**:79-84 (Jan.) 1944.

54. Sophian, L. H.: A Case of Acute Meningitis Caused by Neisseria Perflava, Am. J. M. Sc. **207**:376-378 (March) 1944.

55. Hardy, A. V., and Watt, J.: The Acute Diarrheal Diseases, J. A. M. A. **124**:1173-1179 (April 22) 1944.

55a. Callender, G. R.: Diarrheal Diseases, Am. J. Trop. Med. **24**:7-15 (Jan.) 1944.

56. Smith, H. G.: Sulphaguanidine for Flexner Dysentery, Brit. M. J. **1**:287-289 (Feb. 26) 1944.

strains. Little information is at hand concerning the effect of sulfonamide compounds in severe Shiga infections, for which they are needed most. Attempts to control an outbreak of bacillary dysentery by giving sulfonamide compounds prophylactically to all persons in a group were unsuccessful. The authors favor the use of soluble compounds, such as sulfadiazine, rather than of poorly absorbed ones, like sulfaguanidine.

Differential diagnosis of acute diarrheal diseases can be made with certainty only by isolating the causative agent. The agglutination test with the patient's serum is unreliable. Although the authors say that "Shigella paradysenteriae infection is to be considered as the most probable diagnosis for endemic acute diarrhea," exceptions do occur. From one army camp, for example, Adams and Atwood [57] report 251 cases of bacillary dysentery and 750 cases classified as instances of acute diarrhea or gastroenteritis. In late 1943 epidemic diarrhea of unknown cause was far more prevalent than bacillary dysentery.

Kinnaman and Beelman [57a] report an epidemic of bacillary dysentery involving 3,000 persons, one of the largest, if not the largest, city water-borne outbreaks on record. However, the published bacteriologic data regarding the cause as dysentery bacilli are unconvincing, and one must seriously consider the rumor mentioned in the paper of large numbers of cases of epidemic diarrhea of unknown cause in neighboring communities at the same time.

Together with many others, I have always been skeptical of the stated therapeutic effectiveness of bacteriophage because of the inhibitory effect of blood, pus and tissue débris on its action. New evidence,[58] however, shows that it not only multiplies in animal tissues but is effective in reducing the mortality among mice infected intracerebrally with dysentery bacilli from 96 to 28 per cent. The bacteriophage rapidly accumulated in the infected brain tissue. The equivalent dose of bacteriophage filtrate for man would be about 3 liters. Clinical experience, however, continues to be unpromising.

In tests made by Boyd and Portnoy [59] with bacteriophage highly effective against dysentery bacilli in the test tube, no beneficial effect was noted in patients with dysentery who received it as compared with control patients.

Typhoid.—By using the bacteriophage method of typing, an epidemic of typhoid caused by type C typhoid bacilli was traced to cheese from a local factory and to contacts with the patients.[60] A dairy farmer who supplied milk to the factory was found to carry type C bacilli and probably served as the source of infection. Two patients sick at the same time were found to be infected by type A bacilli and were therefore not part of the epidemic. These infections were traced to carriers of type A bacilli.

According to Callender and Luippold,[61] typhoid and paratyphoid thus far are of little importance in World War II. They conclude that the triple typhoid vaccine now used is superior to that used during World War I. One might add that sanitary conditions, food and water supply in particular, are better than ever before.

Luippold [62] reports greater antigenic effectiveness of a vaccine prepared with a variety of Salmonella, and of a Vi immunogen extracted therefrom, against moderate test doses of typhoid bacilli than of vaccine made from the same strain of typhoid bacilli. In spite of the extrageneric source of this antigen, it may serve to fortify the conventional antityphoid vaccine.

Salmonella Infections.—Bornstein [63] reviews the problem of infections caused by the genus Salmonella. Human disease results either from bacterial invasion, as "salmonella fever," resembling mild typhoid and bacteremia, or from ingestion of the toxin as developed in contaminated food, which result in a true toxemia manifested as gastroenteritis or food poisoning. Prophylaxis depends chiefly on avoiding contaminated food or, better still, preventing contamination of food. Neter reports a case of meningitis caused by S. cholerae suis and reviews others.[64]

57. Adams, J. H., and Atwood, R. T.: Bacillary Dysentery: A Bacteriologic and Clinical Analysis of 251 Cases Occurring in An Army Camp, War Med. **5**:14-20 (Jan.) 1944.

57a. Kinnaman, C. H., and Beelman, F. C.: An Epidemic of Three Thousand Cases of Bacillary Dysentery Involving a War Industry and Members of the Armed Forces, Am. J. Pub. Health **34**:948-954 (Sept.) 1944.

58. Dubos, R. J.; Strauss, J. H., and Peirce, C.: The Multiplication of Bacteriophage in Vivo and Its Protective Effect Against Experimental Infection with Shigella Dysenteriae, J. Exper. Med. **78**:161-168 (Sept.) 1943.

59. Boyd, J. S. K., and Portnoy, B.: Bacteriophage Therapy in Bacillary Dysentery, Tr. Roy. Soc. Trop. Med. & Hyg. **37**:243-262 (Feb.) 1944.

60. Schlesinger, E. R.: Use of Modern Laboratory Aids in the Investigation of a Typhoid Fever Outbreak, Am. J. Pub. Health **33**:1257-1262 (Oct.) 1943.

61. Callender, G. R., and Luippold, G. F.: The Effectiveness of Typhoid Vaccine Prepared by the U. S. Army, J. A. M. A. **123**:319-321 (Oct. 9) 1943.

62. Luippold, G. F.: Antityphoid Activity of Vi Antigen from Extra-Generic Sources, Science **99**:497-498 (June 16) 1944.

63. Bornstein, S.: The State of the Salmonella Problem, J. Immunol. **46**:439-496 (June) 1943.

64. Neter, E.: Salmonella Cholerae Suis Meningitis, Arch. Int. Med. **73**:425-429 (May) 1944.

Salmonella organisms may apparently reside in the abdominal lymph nodes as commensals, since Varela and Olarte [65] found 27 strains in 171 persons at necropsy.

Mice immunized with moccasin venom were protected against the endotoxin of Salmonella typhi murium, and the reverse was also demonstrated.[66] The cross protection may be due to the presence of a common factor in these two poisons of such diverse origin.

Tuberculosis.—Some years ago Lurie's extensive studies showed that the resistance of rabbits to naturally or artificially acquired tuberculosis was in the main controlled by genetic influences. These observations are confirmed in studies of 308 pairs of human twins in which the morbidity rate revealed that the chance of becoming tuberculous increased in direct proportion to the degree of blood relationship to a tuberculous patient.[67] These studies are of especial interest in relation to the ones by Wilson showing the effect of heredity in rheumatic fever, as discussed on page 305.

According to Medlar and his associates,[68] many physicians believe that there are healthy carriers of tubercle bacilli, but they object to the term "healthy carrier" and feel that such persons should be regarded as persons having "occult" tuberculosis in whom disease may follow when their resistance is reduced. Mistake must not be made in regarding all acid-fast bacteria found in sputum as tubercle bacilli. As others have shown, harmless acid-fast bacilli often reside on fruit and vegetables and have no significance if found in gastric washings unless they are proved by culture or animal inoculation to be tubercle bacilli. The authors found acid-fast bacilli in 6 per cent of 548 patients considered nontuberculous; of 17 strains of acid-fast bacilli isolated from the sputum of as many patients, only 4 were pathogenic tubercle bacilli. Since acid-fast bacilli other than tubercle bacilli are more often found in pulmonary lesions than in normal lungs, a degree of pathogenicity may be suspected for them or they may be saprophytes living in damaged tissue.

Complete and permanent absence of tubercle bacilli from the sputum is rarely attained in persons who have suffered from widespread pulmonary tuberculosis, even though they are clinically well and able to do their usual work.[69]

For such persons, although the possibility of endogenous spread is always present, there is little danger from the rare bacilli either to themselves or to others. Occasionally showers of bacilli appear in sputum with no other evidence of trouble. No method of treatment is especially effective in causing continuous absence of bacilli.

Lurie [70] presents evidence that ultraviolet irradiation of the air containing suspended tubercle bacilli prevents the development of tuberculosis in rabbits which otherwise would become infected. The method may be useful in controlling airborne contagion of human tuberculosis.

Attempts in Jamaica [70a] to prevent tuberculosis by vaccination with heat-killed tubercle bacilli were unsuccessful during a period of twenty-one months' observation.

Chemotherapy with Sulfonamide Compounds.—Further report by Feldman and his associates [71] continues to show the value of chemotherapy for experimental tuberculosis. In guinea pigs infected with tubercle bacilli, 28 per cent of those treated with 4,4′ diaminodiphenylsulfone died, as compared with 71 per cent of untreated ones. Prolonged therapy was superior to short term treatment.

The Committee on Therapy of the American Trudeau Society [72] decided that there is as yet inadequate evidence to permit any evaluation of the effect of chemotherapy with sulfonamide compounds on human tuberculosis. They deprecate optimistic articles on the subject in lay magazines.

65. Varela, G., and Olarte, J.: Salmonella Isolated from Human Mesenteric Lymph Nodes, Science **99**: 407-408 (May 19) 1944.

66. Zahl, P. A., and Hutner, S. H.: A Cross-Protective Reaction Between Moccasin Venom and the Endotoxin of Salmonella Typhimurium, Proc. Soc. Exper. Biol. & Med. **55**:134-136 (Feb.) 1944.

67. Kallmann, F. J., and Reisner, D.: Twin Studies on Genetic Variations in Resistance to Tuberculosis, J. Hered. **34**:269-276 (Sept.); 293-301 (Oct.) 1943.

68. Medlar, E. M.; Ordway, W. H., and Pesquera, G. S.: Acid-Fast Bacilli in Patients of a Nontuberculous Medical Service, Am. Rev. Tuberc. **48**:304-313 (Nov.) 1943.

69. Pottenger, F. M., and Pottenger, J. E.: What Is the Clinical and Epidemiological Significance of Rare Bacilli in Sputum? Am. Rev. Tuberc. **48**:279-296 (Nov.) 1943.

70. Lurie, N. B.: Experimental Epidemiology of Tuberculosis: The Prevention of Natural Air-Borne Contagion of Tuberculosis in Rabbits by Ultraviolet Irradiation, J. Exper. Med. **79**:559-572 (June) 1944.

70a. Wells, C. W., and Flahiff, E. W.: Results Obtained with Heat-Killed Tubercle Bacilli Administered to Persons in a General Population, Am. J. Hyg. **40**:109-115 (Sept.) 1944.

71. Feldman, W. H.; Hinshaw, H. C., and Moses, H. E.: The Effects on Experimental Tuberculosis of 4,4′ Diamino-Diphenylsulfone, Am. J. M. Sc. **207**:290-305 (March) 1944.

72. Report of the Committee on Therapy, American Trudeau Society, Am. Rev. Tuberc. **49**:391 (April) 1944.

Leprosy.—Although previous experience led to somewhat pessimistic conclusions, Faget and his co-workers [73] now regard promin (the sodium salt of p,p-diaminodiphenylsulfone-N,N-didextrose sulfonate) the most promising drug in the treatment of leprosy. While there is no direct evidence that the drug affects the bacillus of leprosy and in no treated patient has the disease been arrested, it appeared to slow the progress of the disease in a considerable number of patients.

Cholera.—Huang [74] had success in the treatment of cholera with sulfaguanidine. Only 1 death among 22 patients was reported, in contrast to the usual reported mortality rate of 20 to 60 per cent. No control untreated patients are included in the report, and no confirmative bacteriologic studies are mentioned. The results are therefore of interest but not convincing.

Plague.—According to Pollitzer and Li,[75] control measures and seasonal influence are not the only factors which limit an outbreak of pneumonic plague. In the study of an outbreak in North Hunan, China, in 1942, the last patients observed before the epidemic abated spontaneously had little or no cough or sputum. Because cough and bacillus-laden sputum are the sources of infection, they believe that the occurrence of a preponderance of cases of "non-pneumonic" lung pest is an important factor in the decline of epidemics.

Because of the divergence in opinion regarding the value of sulfonamide compounds for human beings with plague, experiments were made [76] on guinea pigs infected in a manner similar to that which occurs in human disease. Sulfadiazine was effective in preventing death in a high proportion of animals as compared with untreated controls. The drug should be given as soon as the buboes appear.

Whooping Cough.—In a well controlled study in Iceland,[77] where the epidemiology of whooping cough is relatively simple because of its appearance in epidemics at long intervals, an unusual opportunity arose to test the value of vaccination. The following results in percentage were recorded from studies of 888 vaccinated and 122 unvaccinated children:

	Vaccinated	Unvaccinated
No pertussis	28	5
Mild pertussis	49	49
Medium pertussis	17	34
Grave pertussis	5	11

Since all the children were in all probability equally exposed to infection, the authors believe from the results shown that vaccination is of undoubtable value.

Melioidosis.—The second case of chronic melioidosis in a European is reported.[78] The diagnosis is easily confused with tuberculosis unless the causative bacillus, Pfeifferella whitmori, is found. The disease is one which affects both rodents and human beings and is thought to be related to glanders, which it also resembles. The infection may be important to military personnel serving in the Far East where it occurs.

DISEASES CAUSED BY FILTRABLE VIRUSES

Poliomyelitis. — Editorial comment [79] on a paper by Maxey and Howe is criticized by several authorities [80] on the subject of poliomyelitis, who do not believe contact infection to be the most important means of spreading the disease as stated. The mode of spread is indeed baffling; transmission may occur through water supply, fecal contamination, insects or air or by contact. Although the editorial advises rigid measures to prevent contact infection, the critics point out the futility of these procedures because for every easily recognized patient with paralysis there are 10 or more with mild or inapparent forms which are seldom correctly diagnosed and which may also serve as sources of infection.

Even known cases are often not reported, so that official statistics may vary greatly as regards the incidence of the disease and its fatality rate. In Massachusetts 23 per cent of a group of 2,200 patients were not reported to health authorities.[80a]

73. Faget, G. H.; Pogge, R. C.; Johansen, F. A.; Dinan, J. F.; Prejean, B. M., and Eccles, C. G.: The Promin Treatment of Leprosy: A Progress Report, Pub. Health Rep. **58**:1729-1741 (Nov. 26) 1943.

74. Huang, J.: Treatment of Asiatic Cholera with Sulfaguanidine: Clinical Study of Twenty-Two Cases, J. A. M. A. **125**:24-25 (May 6) 1944.

75. Pollitzer, R., and Li, C. C.: Some Observations on the Decline of Pneumonic Plague Epidemics, Chinese M. J. **61**:212-216 (July-Sept.) 1943.

76. Wayson, N. E., and McMahon, M. C.: Plague: Sulfadiazine Treatment of Guinea Pigs Infected by Artificial Methods or by Flea Transmission, Pub. Health Rep. **59**:385-393 (March 24) 1944.

77. Dungal, N.; Thoroddsen, S., and Ágúston, H.: Vaccination Against Whooping Cough, J. A. M. A. **125**:200-202 (May 20) 1944.

78. Mayer, J. H., and Finlayson, M. H.: Chronic Melioidosis: Case Showing Bone and Pulmonary Lesions, J. Roy. Army M. Corps **82**:4-13 (Jan.) 1944.

79. The Modes of Spread of Infantile Paralysis, editorial, J. A. M. A. **123**:904 (Dec. 4) 1943.

80. Ward, R., and Melnick, J. L.: Spread of Infantile Paralysis, Correspondence, J. A. M. A. **124**:595-596 (Feb. 26) 1944. Paul, J. R.: Spread of Infantile Paralysis, Correspondence, ibid. **124**:596 (Feb. 26) 1944.

(Footnotes continued on next page)

Harmon and Hoyne,[81] citing 2 case reports, point out that infantile paralysis is never transmitted to the fetus in utero. The virus is seldom if ever present in the blood. Poliomyelitis occurs during the cold winter months, and the virus can be found in the intestinal contents of both patients and healthy carriers.[82] Flies were obviously not transmitters of the infection in these cases. The patient and the healthy carrier serve as reservoirs of infection, which is no doubt disseminated by several methods.

Recent studies again bring the question of airborne infection into prominence. Poliomyelitis virus was present in material swabbed from the throats of 7 of 14 patients in the first week of the disease.[82a] Furthermore, the disease can be transmitted with ease to monkeys by placing them in a chamber into which the virus is sprayed.[82b]

Although Sister Kenny's method for the treatment of poliomyelitis was widely acclaimed as an advance in the treatment of infantile paralysis, her unusual concepts regarding the disease and even the value of her methods have been the subject of doubt and of inquiry. In a critical study Moldaver[83] finds, contrary to Kenny's view, that spasm is not the most damaging symptom. Furthermore, in alienated muscles there is neither functional paralysis nor physiologic block. These muscles lose their power partially or completely because the anterior horn cells are damaged or destroyed. In the paralytic muscle regarded as alienated there is always some degeneration. Incoordination does not consist of misdirection of nerve impulses. It is caused, if at all, by the inability of partially or totally alienated muscles to respond.

In electromyographic studies[84] Kenny's theories of spasm and mental alienation were found to be insufficient and misleading. The existence of incoordination was the only condition upheld by the tests.

In other studies[85] there is agreement that spasm does not arise chiefly within the muscle but is a reflex phenomenon. The spasm is apparently neurogenic and results from blocking of the reflexes by lesions in the gray matter of the cord.

According to Sherman,[86] in the enthusiasm for the Kenny treatment sight is lost of the natural history of the disease. She points out that the severity of poliomyelitis varies greatly from time to time. As so often happens, cases of mild poliomyelitis in which paralysis would not develop anyway are included in statistics purporting to show the benefit of any form of treatment. In a study of an epidemic group of 70 cases in Chicago in which the Kenny treatment was not used, 10 per cent of the patients had residual weakness, 73 per cent had no residual weakness, 8 per cent had significant weakness and 8 per cent died. These results compare favorably with those in cases in which the Kenny treatment was applied. No specific effect was noted from the use of blood of convalescent adults in 53 patients. The author again calls attention to the fact that the amount of ultimate recovery from poliomyelitis depends primarily on the amount of initial injury to the central nervous system.

About the only good thing a special committee of investigation[87] of the Kenny treatment has to say about it is that interest in the disease has been stimulated and various known methods of treatment have been reevaluated. According to the committee there is no evidence that the Kenny treatment prevents or decreases the amount of paralysis. Sister Kenny and her supporters have evidently been led astray by including in their statistical reports cases of mild forms of the dis-

80a. Nelson, N. B., and Aycock, W. L.: A Study of the Reporting of Paralytic Poliomyelitis in Massachusetts 1928-1941, Am. J. Hyg. **40**:113-169 (Sept.) 1944.

81. Harmon, P. H., and Hoyne, A.: Poliomyelitis and Pregnancy with Special Reference to the Failure of Fetal Infection, J. A. M. A. **123**:185-187 (Sept. 25) 1943.

82. Ward, R., and Sabin, A. B.: The Presence of Poliomyelitis Virus in Human Cases and Carriers During the Winter, Yale J. Biol. & Med. **16**:451-459 (May) 1944.

82a. Howe, H. A.; Wenner, H. A.; Bodian, D., and Maxey, K. F.: Poliomyelitis Virus in the Human Oro-pharynx, Proc. Soc. Exper. Biol. & Med. **56**:171-172 (June) 1944.

82b. Faber, H. K.; Silverberg, R. J., and Dong, L.: Poliomyelitis in the Cynomolgous Monkey, J. Exper. Med. **80**:39-57 (July) 1944.

83. Moldaver, J.: Physiopathologic Aspect of the Disorders of Muscles in Infantile Paralysis: Preliminary Report, J. A. M. A. **123**:74-77 (Sept. 11) 1943.

84. Watkins, A. L.; Brazier, M. A. B., and Schwab, R. S.: Concepts of Muscle Dysfunction in Poliomyelitis Based on Electromyographic Studies, J. A. M. A. **123**:188-192 (Sept. 25) 1943.

85. Bouman, H. D., and Schwartz, R. P.: The Degree, the Extent and the Mechanism of Muscle Spasm in Infantile Paralysis, New York State J. Med. **44**:147-153 (Jan. 15) 1944. Kabat, H., and Knapp, M. E.: The Mechanism of Muscle Spasm in Poliomyelitis, J. Pediat. **24**:123-127 (Feb.) 1944.

86. Sherman, M. S.: The Natural Course of Poliomyelitis: A Report of Seventy Cases, J. A. M. A. **125**: 99-102 (May 13) 1944.

87. Ghormley, R. K.; Compere, E. L.; Dickson, J. A.; Funsten, R. V.; Key, J. A.; McCarroll, H. R., and Schumm, H. C.: Evaluation of the Kenny Treatment of Infantile Paralysis: Report of Committee, J. A. M. A. **125**:466-469 (June 17) 1944.

ease in which recovery without paralysis would have occurred spontaneously.

While it may be reasonable to assume that a normal diet adequate in vitamins would serve as a protection against infection, in experimental studies this is not borne out. Actually, animals on a diet deficient in thiamine were more resistant to infection with poliomyelitis virus [88] and with Theiler's virus [89] than those on an adequate diet. In other similar studies the results were not conclusive.[90] Mice fed a diet deficient only in calcium pantothenate were less resistant to infection with Theiler's virus than mice fed an adequate diet but had the same resistance to the Lansing strain of poliomyelitis.[91] One suggestion to account for this paradox assumes that the vitamins and other nutritional needs of the virus are greater than those of the normal tissue cells. A decrease in the amount of lactic acid in the brain in poliomyelitis suggests that the virus interferes in a specific manner with metabolism of the cells.[92] Evidence obtained with the electron microscope [93] suggests that the virus of poliomyelitis is composed of threadlike particles 15 to 35 millimicrons wide and 250 millimicrons long.

Howard [94] collected reports of 259 cases in which poliomyelitis, mostly bulbar, followed tonsillectomy within sixty days. This operation should not be performed when poliomyelitis is prevalent. A correlation exists between the absence of pharyngeal lymphoid tissue and involvement of the higher centers in poliomyelitis. The absence of tonsils and adenoids apparently increases the risk of bulbar involvement in patients with poliomyelitis.[94a]

Relationship with Other Viruses.—From an epidemic of poliomyelitis in the British Army, which was confused with encephalitis, two different strains of virus were obtained.[95] One was similar to the Lansing type, and the other was not. Gard,[96] in Sweden, who has reported the purification of poliomyelitis viruses, believes the viruses of human poliomyelitis, of mouse encephalomyelitis of Theiler and of infectious swine paralysis (Teschen disease) to be identical except for their species specificity.

Other studies [97] also suggest an intimate relationship between the viruses of poliomyelitis in man and Theiler's poliomyelitis of mice. The morphologic nature of the simian or mouse-adapted strains of poliomyelitis virus and of Theiler's virus is the same; there is evidence of antigenic relationship, and the lesions caused by the Lansing strain of poliomyelitis are the same as those caused by the mouse virus.

Jungeblut also isolated two strains of poliomyelitis, one from a child and one from a mouse in the child's home, both of which caused paralysis in inoculated rodents. Both were neutralized by antiserum made with Theiler's virus. The latter virus, which is ordinarily not pathogenic in guinea pigs or monkeys, was caused to become so by passage through cotton rats. The changed characteristics were apparently permanent. Further evidence of the instability or variability of filtrable viruses comes from work on Theiler's virus.[98] Rapid passage of strains of this virus in mice induces on certain occasions the appearance of a variant form which differs from the parent strain by its power to invade the central nervous system from peripheral channels. The variant form retained its characteristics on further passage, but it is antigenically identical with the noninvasive parent strain. These interesting experiments raise the question discussed later

88. Foster, C.; Jones, J. H.; Henle, W., and Durfman, F.: The Effect of Vitamin B_1 Deficiency and of Restricted Food Intake on the Resistance of Mice to the Lansing Stain of Poliomyelitis Virus, J. Exper. Med. **79**:221-234 (Feb.) 1944.

89. Rasmussen, A. F.; Waisman, H. A.; Elvehjem, C. A., and Clark, P. F.: Influence of the Level of Thiamine Intake on the Susceptibility of Mice to Poliomyelitis Virus, J. Infect. Dis. **74**:40-47 (Jan.-Feb.) 1944.

90. Toomey, J. A.; Frohring, W. D., and Takacs, W. S.: Vitamin B_1 Deficient Animals and Poliomyelitis, Yale J. Biol. & Med. **16**:477-485 (May) 1944.

91. Lichstein, H. C.; Waisman, H. A.; Elvehjem, C. A., and Clark, P. F.: Influence of Pantothenic Acid Deficiency on Resistance of Mice to Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **56**:2-5 (May) 1944.

92. Kabat, H.; Erickson, D.; Eklund, C., and Nickle, M.: Decrease in Lactic Acid Content of the Brain in Poliomyelitis, Science **98**:539-591 (Dec. 31) 1943.

93. Melnick, J. L.: Detection with the Electron Microscope of Rod Shaped Particles in Stools of Normal and Poliomyelitic Individuals, J. Immunol. **48**: 25-28 (Jan.) 1944.

94. Howard, R. E.: Relationship of Poliomyelitis to Tonsillectomy, Ann. Otol., Rhin. & Laryng. **53**:15-25 (March) 1944.

94a. Lucchesi, P. F., and La Bocetta, A. C.: Relationship of Tonsils and Adenoids to Type of Poliomyelitis: Analysis of 432 Cases, Am. J. Dis. Child. **68**:1-4 (July) 1944.

95. Schlesinger, R. W.; Morgan, I. M., and Olitsky, P. K.: Transmission to Rodents of Lansing Type Poliomyelitis Virus Originating in Middle East, Science **98**:452-454 (Nov. 19) 1943.

96. Gard, S.: Purification of Poliomyelitis Viruses: Experiments on Murine and Human Strains, Acta med. Scandinav., 1943, supp. 143; editorial, J. A. M. A. **124**:578 (Feb. 26) 1944.

97. Jungeblut, C. W.: Biological Changes in Theiler's Virus of Spontaneous Mouse Encephalomyelitis, Am. J. Pub. Health **33**:1227-1243 (Oct.) 1943.

98. Jungeblut, C.: Variability of Theiler's Virus of Mouse Encephalomyelitis, Science **99**:434-435 (May 26) 1944.

concerning influenza virus and the psittacosis group of viruses and leave little doubt that, like bacteria, viruses which are descendants of a common parent may dissociate into various strains of different behavior. It may also be asked if certain distinct but similar types may exist and persist without necessarily a change from one form to another. These views bring out striking analogies with the variable agents of typhus, Rocky Mountain spotted fever, brucellosis, tularemia, influenza and other diseases which may also affect human beings, rodents and swine; show important reciprocal transmissibility of diseases of animals and human beings, and suggest that all microbes behave in a similar manner.

Encephalitis.—The questions just raised may also apply to the three immunologically distinct neurotropic virus diseases known as Eastern equine encephalomyelitis, Western equine encephalomyelitis and Venezuelan equine encephalomyelitis. All three affect horses and man and are similar in other respects. The Venezuelan strain is identical with the one known in horses in Colombia since 1935. It is also present in Ecuador and Trinidad [99] and probably elsewhere as well. Thus far, however, only 1 "natural" infection has been proved in man,[100] and 10 cases in which the infection was contracted during laboratory studies have been reported.[101] It is probable that more such infections in human beings occur in endemic centers but have thus far been mistaken for other diseases or unnoticed. In support of this view, specific neutralizing antibodies were demonstrated in the serum of 9 of 10 persons who had handled the virus and who had had a mild disease diagnosed as grip.[102] While it is believed that this group of neurotropic virus diseases is included among the arthropod-borne encephalitides, the fact that the Venezuelan virus could be easily isolated from the throat washings from 2 patients suggests that there are other means of transmission as well. Both Eastern and Western encephalomyelitis occurs among horses and mules in South America.[103]

It is well known that in the United States an etiologic diagnosis can be made in only about 10 per cent of cases of encephalomyelitis. Moreover, the clinical signs and symptoms even among known entities are so similar that differentiation can be made only in the laboratory. In a study [104] of 75 cases of disease of the central nervous system in Chicago, 9 infections were apparently caused by the virus of lymphocytic choriomeningitis, as discovered by making special tests in retrospect.

In a study to determine the relationship of several newly discovered neurotropic viruses, of Russian spring-summer encephalitis, louping ill and Western equine encephalitis, to the viruses of Japanese B, St. Louis and West Nile types of encephalitis, Casals [105] reports as follows: The viruses of Russian encephalitis and louping ill are closely related to each other in some respects and not in others, and neither is related to the rest of the viruses studied. The Japanese B, St. Louis and West Nile viruses show a degree of relationship as a group. Western equine encephalitis virus was unrelated to any of the others.

In most cases the heterologous reactions between viruses were weaker than the homologous ones, which is helpful in diagnosis between any two closely related viruses. As in the case of bacteria, different viruses may exhibit a close degree of similarity and relationship, probably even closer than bacteria because of the apparent simpler constitution of viruses and hence the greater opportunity for the same structure to repeat itself in different viruses.

Hayes and Hartmann [106] report a case of lymphocytic choriomeningitis acquired in the laboratory in which systemic symptoms with pneumonia were predominant. No evidence of invasion of the central nervous system appeared. The diagnosis in the absence of etiologic data would have been grip, bronchitis or pneumonia. A case of recurrent lymphocytic choriomenin-

99. Kubes, V.: Venezuelan-Type Equine Encephalomyelitis Virus in Trinidad, Science **99**:41-42 (Jan. 14) 1944.

100. Randall, R., and Mills, J. W.: Fatal Encephalitis in Man Due to the Venezuelan Virus of Equine Encephalomyelitis in Trinidad, Science **99**:225-226 (March 17) 1944.

101. Casals, J.; Curnen, E. C., and Thomas, L.: Venezuelan Equine Encephalomyelitis in Man, J. Exper. Med. **77**:521-530 (June) 1943. Lennette, E. H., and Koprowski, H.: Human Infection with Venezuelan Equine Encephalomyelitis Virus: A Report on Eight Cases of Infection Acquired in the Laboratory, J. A. M. A. **123**:1088-1095 (Dec. 25) 1943.

102. Gallia, F., and Kubeš, V.: Neutralization of the Venezuelan Encephalomyelitis Virus by Human Serum, J. A. M. A. **125**:894-897 (July 29) 1944.

103. Identity of Equine Encephalomyelitis Virus in Brazil and in the United States, Foreign Letters, J. A. M. A. **124**:727 (March 11) 1944.

104. Milzer, A.: Neurotropic Virus Infections in Chicago, 1939-1941: Nine Cases of Lymphocytic Choriomeningitis, Proc. Soc. Exper. Biol. & Med. **54**: 279-282 (Dec.) 1943.

105. Casals, J.: Immunological Relationship Among Central Nervous System Viruses, J. Exper. Med. **79**: 341-359 (April) 1944.

106. Hayes, G. S., and Hartmann, T. L.: Lymphocytic Choriomeningitis: Report of a Laboratory Infection, Bull. Johns Hopkins Hosp. **73**:275-286 (Oct.) 1943.

gitis [107] and one caused by the virus of herpes simplex [108] are reported.

Eight cases of encephalomyelitis occurred among 53,000 persons in Scotland vaccinated against smallpox, an incidence, as stated, of 1 to 6,600.[109] The probabilities are that the incidence would have been much higher if mild attacks had been recognized and included. The mortality rate in the recognized cases was 44 per cent.

A newly discovered virus, Semliki Forest virus, was discovered in Africa during studies on yellow fever.[109a] It was isolated from mosquitoes and found to cause encephalitis in laboratory animals. It may cause disease in man since specific immune bodies were demonstrable in natives. The virus is different from other known ones but may be similar to that of Russian spring-summer encephalitis.

Interference Phenomena.—When the virus of equine encephalomyelitis is injected into chick embryos already infected with St. Louis encephalitis virus, it grows only slightly, if at all.[110] Similarly, influenza virus interferes with the growth of the same virus. These results are analogous with those reported many years ago by Breinl with Rocky Mountain spotted fever and typhus rickettsias, with those of Aronson and Meranze on tuberculosis and syphilis and with those of different culture phases of influenza virus itself, as mentioned on page 296.

Rabies.—Shaughnessy and Zichis [111] attempted to duplicate in guinea pigs the events which occur when human beings are bitten by rabid animals in order to study the relative effects of methods of treatment of wounds. Since the majority of persons bitten by rabid dogs do not contract rabies, the procedure of applying caustics to the area of the bite has persisted, since it was probably given credit for preventing the infection in persons who would have escaped anyway. According to the experiments, irrigation of the wound with 20 per cent solution of medicinal soft soap was just as effective as fuming nitric acid, if not more so, if used within a few hours. Sulfanilamide and tincture of iodine were of no value.

Measles.—In Swyer's [112] experience with 1,193 cases of measles, a short course of chemoprophylaxis was not found to be worth while. Complications, such as bronchopneumonia and otitis media, were treated as they arose.

Mumps.—Enders [113] demonstrated specific antibodies in 92 per cent of persons who had had mumps. Antibodies were also present in 50 per cent of persons who were unaware of having had the disease, suggesting that they had had inapparent or unrecognized infection. Persons without antibodies are presumably susceptible to the disease. A cutaneous test was developed which indicates previous infection with the virus.

Yellow Fever.—In a study to find the source of jungle yellow fever, observers [114] in Colombia found that the virus may be sustained among monkey or marsupial populations or a mixture of the two, but there is no mammalian reservoir of yellow fever virus. The virus may persist in mosquitoes during their lifetime, hence the true reservoir exists in the mosquito vector, not in the mammalian part of the cycle. The infection caused no illness in animals, and the virus persists in their blood only a few days. The mosquitoes involved are arboreal and live from one rainy season to the next, thus perpetuating the virus.

Experience in Colombia [115] attests to the value of prophylactic vaccination against yellow fever. Among 600,000 persons vaccinated with the 17D strain, only 1 was recognized as acquiring the disease. In contrast to this, and in the same area and time period, between 1937 and 1943, 198 proved and 45 probable infections occurred in unvaccinated persons. The immunity induced by vaccination apparently lasted four years.

Antigen prepared from infected mouse brains appears to be the one of choice for the complement fixation test in the diagnosis of yellow

107. Treusch, J. V.; Milzer, A., and Levinson, S. O.: Recurrent Lymphocytic Choriomeningitis, Arch. Int. Med. **72**:709-714 (Dec.) 1943.

108. Zarafonetis, C. J. D.; Smadel, J. E.; Adams, J. W., and Haymaker, W.: Fatal Herpes Simplex Encephalitis in Man, Am. J. Path. **20**:429-441 (May) 1944.

109. Fyfe, G. M., and Fleming, J. B.: Encephalomyelitis Following Vaccination in Fife, Brit. M. J. **2**: 671-673 (Nov. 27) 1943.

109a. Smithburn, K. C., and Haddow, A. J.: Semliki Forest Virus: I. Isolation and Pathogenic Properties, J. Immunol. **49**:141-158 (Sept.) 1944.

110. Duffy, C. E.: Interference Between St. Louis Encephalitis Virus and Equine Encephalomyelitis Virus (Western Type) in the Chick Embryo, Science **99**:507-518 (June 23) 1944.

111. Shaughnessy, H. J., and Zichis, J.: Prevention of Experimental Rabies: Treatment of Wounds Contaminated by Rabies Virus with Fuming Nitric Acid, Soap Solution, Sulfanilamide or Tincture of Iodine, J. A. M. A. **123**:528-533 (Oct. 4) 1943.

112. Swyer, R.: Use of Sulfonamides in Measles, Brit. J. Child. Dis. **40**:63-67 (July-Sept.) 1943.

113. Enders, J. F.: Observations on Immunity in Mumps, Ann. Int. Med. **18**:1015-1025 (June) 1943.

114. Bugher, J. C.; Boshell-Manrique, J.; Roca-Garcia, M., and Osorno-Mesa, E.: Epidemiology of Jungle Yellow Fever in Eastern Colombia, Am. J. Hyg. **39**:16-51 (Jan.) 1944.

115. Bugher, J. C., and Gast-Galvis, A.: The Efficacy of Vaccination in the Prevention of Yellow Fever in Colombia, Am. J. Hyg. **39**:58-66 (Jan.) 1944.

fever.[116] It is biologically specific, is of uniform potency and can be prepared fresh when needed.

Blattner and his associates[117] isolated a filtrable virus from a patient with Kaposi's varicelliform eruption by inoculating fluid from the vesicles on the corneas of rabbits and subsequently establishing the strain in mice and in egg cultures.

Influenza.—Sporadic cases of influenza A occurred in the Middle West before the epidemic appeared elsewhere in the winter of 1943.[118] A certain proportion of influenza-like infections of the respiratory tract also occurred which were apparently not caused by either A or B influenza virus. In a study[119] of epidemics of infection of the respiratory tract in a Canadian army camp, the composite nature of these epidemics was again noted. Some waves of disease were caused by influenza virus A, some by virus B and some by unknown agents. Others apparently included the common cold and the syndrome "viral" pneumonia. In most epidemics varying combinations of these similar yet etiologically different infections were present. In an editorial in the *Lancet*,[120] three English reports were reviewed. What little influenza occurred in England in 1943 was caused by B virus, and none of the outbreaks was widespread or severe. Severe epidemics are usually caused by A virus. B virus is more difficult to isolate from patients than A virus. British workers reaffirmed their view that the particles of influenza virus were about 80 millimicrons in diameter. Previous estimates of 10 to 15 millimicrons based on measurements with the electron microscope were apparently made by various workers on the wrong particles, which were mistaken for those of the virus. Sharp and his co-workers[121] found by electron micrography that influenza virus B was composed of spherical or ovoid bodies measuring 98 millimicrons, which is somewhat larger than the kidney-bean–shaped particles of A virus.

It is possible[122] to isolate the virus of influenza A from throat washings of patients by direct inoculation of the developing chick embyro.

According to Hirst's[123] experiments, the virus of influenza A when inoculated intratracheally into ferrets is rapidly absorbed by the pulmonary epithelial cells. The virus is apparently attached permanently, and any free virus which is later recoverable is probably the product of multiplication. In perfused lungs the virus is not permanently fixed and is released after several hours, similar to the manner of its release from chicken erythrocytes by elution in the test tube. A specific receptor substance is supposedly involved in the reaction.

Hirst[124] also shows that, contrary to the reports of others, various strains of virus A from widely separated areas are extraordinarily homogeneous according to the chicken red cell test.

In a recent lecture (University of Pennsylvania, Jan. 20, 1944) Burnet discussed the "interference" phenomenon, explainable, he believes, by the attachment of a variant phase of influenza virus to cells, which prevents the invasion of the virus in a different variant phase. Viruses, like bacteria and fungi, appear to have different culture phases, or variants, which have different cultural, immunologic and invasive characteristics. The considerable confusion and divergence in results and opinions in certain experimental work thus far performed with influenza virus probably arise from this source. The culture phase which grows best in an artificial experimental environment may not be the phase actually responsible for human infection or the best antigen for the preparation of vaccine. The severity of a given attack or of an epidemic may depend on the phase of the virus prevalent in a community. This virus in one phase may attack only a few respiratory tract cells to give mild disease, and in another phase may attack all cells to cause severe disease.

Experiments which indirectly support these views were made by Parker and her associates.[125]

116. Lennette, E. H.: The Complement Fixation Test in the Diagnosis of Yellow Fever, Am. J. Trop. Med. **23**:481-504 (Sept.) 1943.

117. Blattner, R. J.; Heys, F. M., and Harrison, M. L. K.: A Filtrable Virus Isolated from a Case of Kaposi's Varicelliform Eruption, Science **99**:432-434 (May 26) 1944.

118. Salk, J. E.; Menke, W. J., and Francis, T., Jr.: Identification of Influenza Virus Type A in Current Outbreak of Respiratory Disease, J. A. M. A. **124**:93 (Jan. 8) 1944.

119. Hare, R.; Hamilton, J., and Feasby, W. R.: Influenza and Similar Respiratory Infection in Military Camp Over Period of Three Years, Canad. J. Pub. Health **34**:453-464 (Oct.) 1943.

120. Influenza, editorial, Lancet **2**:801 (Dec. 25) 1943.

121. Sharp, D. G.; Taylor, A. R.; McLean, I. W.; Beard, D.; Beard, J. W.; Feller, A. E., and Dingle, J. H.: Isolation and Characterization of Influenza Virus B (Lee Strain), Science **99**:307-308 (Oct. 1) 1943; J. Immunol. **48**:129-153 (Feb.) 1944.

122. Thigpen, M., and Crowley, J.: Isolation of Influenza A by Intra-Allantoic Inoculation of Untreated Throat Washings, Science **98**:516 (Dec. 10) 1943.

123. Hirst, G. K.: Absorption of Influenza Virus on Cells of the Respiratory Tract, J. Exper. Med. **78**: 99-110 (Aug.) 1943.

124. Hirst, G. K.: Studies of Antigenic Differences Among Strains of Influenza A by Means of Red Cell Agglutination, J. Exper. Med. **78**:407-423 (Nov.) 1943.

125. Parker, E. R., and MacNeal, W. J.: Persistence of Influenza Virus on the Human Hand, J. Lab. & Clin. Med. **29**:121-126 (Feb.) 1944.

Suspensions of virus made directly from the lungs of influenza-infected mice were easily inactivated by drying, whereas virus from cultures of allantoic membrane retained high potency after drying for several hours. Since virus retains its activity when dried on soiled hands for this long, it is suggested that the disease itself may be transmitted by this means. Washing with soap inactivates the virus.

Other investigations [126] lend further support to the concept of variation. Attempts to infect 24 volunteers with influenza virus in amounts usually capable of causing infection were unsuccessful. The possibility of a change in the invasiveness of the virus during transfer in animals and in eggs was suspected.

Burnet [127] points out that the virus of "Newcastle" disease of fowl in Australia is similar to the influenza viruses. Infection occurred in a laboratory worker when virus accidentally came in contact with the conjunctiva. Fluid from the eye contained the virus, which was cultivated in eggs and agglutinated chicken erythrocytes.

Influenza Vaccine.—Francis and his associates [128] infected a group of persons with a strain of type A influenza virus. Most of them had been vaccinated previously by subcutaneous injection of 1 cc. of vaccine representing the allantoic fluid of fertile hen's eggs infected with both type A and type B virus. As compared with unvaccinated controls, 50 per cent of whom had fever a day or so after inoculation, only 16 per cent had fever. None of the latter had temperatures over 38.1 C. (100.6 F.), whereas 9 of the control group had temperatures of 38.3 C. (101 F.) or more. Those vaccinated over four months before inoculation were considerably less resistant than those vaccinated only two weeks before. Similar results were observed in persons inoculated with type B virus.[129]

In other studies [130] from the same laboratory, human subjects were infected with influenza B virus by inhalation. After an incubation period of twelve to twenty-four hours, 27 of 30 volunteers became sick. Constitutional symptoms predominated; symptoms of involvement of the respiratory tract were inconspicuous. Four months later the group were reinfected with the same virus, together with controls who had not been previously infected. Symptoms again developed in the reinfected subjects, but they were milder. It appeared that a certain degree of residual resistance resulted from the first infection, but if frank infection fails to give uniform staunch resistance it seems likely that attempts to establish immunity with "attenuated" virus or with vaccine would be even less effective. It would seem that if prophylactic procedures of this type are to be effective they must be repeated within four month periods.

The report [131] of a commission to study the value of influenza vaccine states that vaccine given shortly before or shortly after the onset of an epidemic gave protection against the disease. The attack rate was 2 per cent among 6,000 vaccinated persons and 7 per cent among 6,000 control persons, a ratio of 1 : 3.2.

Attempts [132] to protect mice against infection with influenza virus with a variety of chemotherapeutic and antibiotic agents were entirely unsuccessful.

Certain substances, such as dead tubercle bacilli and other acid-fast bacilli, when added to influenza virus vaccine are said [133] not only to enhance its immunizing power but to maintain immunity at a high level for a long period in experimental animals. This finding is interesting in view of other examples of extrageneric relationship of antigen in the Salmonella-typhoid group, discussed on page 289 and in view of the use a few years ago of distemper virus with influenza virus, which has been abandoned.

Respiratory Tract Infection.—The possible effect of sulfonamide compounds in preventing bacterial complications during the common cold was tested by numerous investigators. The results are diverse and confusing, as may be expected in dealing with infections of this type, which vary so greatly in causation and symptoms in different places at the same time and in a given place at different times and even at the same place at the same time. For example, from

126. Krueger, A. P., and others: Experimental Human Influenza, Am. J. M. Sc. **207**:306-313 (March) 1944.

127. Burnet, F. M.: Human Infection with Virus of New Castle Disease of Fowls, M. J. Australia **2**:313-314 (Oct. 16) 1943.

128. Francis, T.; Salk, J. E.; Pearson, H. E., and Brown, P. N.: Protective Effect of Vaccination Against Induced Influenza A, Proc. Soc. Exper. Biol. & Med. **55**:104-105 (Feb.) 1944.

129. Salk, J. E.; Pearson, H. E.; Brown, P. N., and Francis, T.: Protective Effect of Vaccination Against Induced Influenza B, Proc. Soc. Exper. Biol. & Med. **55**:106-107 (Feb.) 1944.

130. Francis, T.; Pearson, H. E.; Salk, J. E., and Brown, P. N.: Immunity in Human Subjects Artificially Infected with Influenza Virus, Type B, Am. J. Pub. Health **34**:317-334 (April) 1944.

131. A Clinical Evaluation of Vaccination Against Influenza: Preliminary Report by the Members of the Commission on Influenza, J. A. M. A. **124**:982-985 (April 1) 1944.

132. Krueger, A. P., and others: Attempts to Protect Against Influenza Virus with Various Sulfonamides, Acridines and Antibiotics, Science **98**:348-349 (Oct. 15) 1943.

133. Friedewald, W. F.: Enhancement of the Immunizing Capacity of Influenza Vaccines with Adjuvants, Science **99**:453-454 (June 2) 1944.

one army post [134] only 25 per cent of attacks of exudative pharyngitis and tonsillitis were caused by hemolytic streptococci; from another group [135] 50 per cent of diseases of the respiratory tract were streptococcic in origin, while in a naval center [136] it is said that the majority of important diseases of the respiratory tract were caused by these bacteria.

Sulfadiazine prophylaxis applied in the two latter groups is said to have reduced the incidence of these infections by 50 to 85 per cent. Impersonal studies and mass statistics involving thousands of subjects in these groups are fraught with interpretative and other difficulties, and the results must be accepted with caution. In more limited observations [137] on tonsillitis, therapy with sulfonamide compounds shortened the course of illness by only one day, which seems hardly worth the discomfort and risk involved in the treatment.

Cecil, Plummer and Smillie [138] conclude that according to the published evidence the exact role of these drugs in the treatment of the common cold is not established. In a controlled test in which sulfadiazine was given orally, the course of uncomplicated common colds was not shortened or altered and no striking effects were observed in complicated colds. Only in certain selected cases was there bacteriologic evidence that secondary infection may be prevented. There was in general a consistent reduction in the total number of pathogenic organisms with 1 Gm. doses of sulfadiazine three times a day. Oral therapy is just as efficient for this purpose as local therapy with a spray.

Much harmful propaganda has appeared advertising a variety of mixtures containing sulfonamide compounds for local intranasal therapy, especially extolling variously sized or shaped microcrystals. Local therapy with any form of sulfonamide compounds is generally deprecated because of (1) the lack of conclusive evidence of beneficial effect in relieving the common cold or in preventing complications or sequels thereof, (2) the possibility of sensitizing patients, so that if sulfonamide compounds are later needed for some serious infection they cannot be given and (3) the possibility of inducing resistance to sulfonamide compounds of pathogenic bacteria which may be present.

Prevention of the Common Cold.—Propylene glycol sprayed into the air of school rooms, particularly if the relative humidity is between 35 and 40 per cent, was effective in reducing the incidence of infections of the upper respiratory tract.[139] In one group studied only 3 colds occurred in persons in the treated atmosphere, as compared with 79 in the control group. In other work,[140] propylene glycol vapor was found bactericidal for pneumococci in a dilution of 1 Gm. to 20,000,000 cc. of air, and for streptococci and staphylococci in a dilution of 1 to 5,000,000 parts, providing the relative humidity was between 45 and 70 per cent.

In one experiment,[140a] ultraviolet irradiation of the air of sleeping quarters failed to influence the number of infections of the respiratory tract. The great variation in the incidence and nature of such infections makes studies of this type difficult to evaluate.

"Cold" Vaccines.—Further data [141] are added to the mass of evidence against the value of vaccines to prevent the common cold. Groups of employees of a large manufacturing plant were given five different forms of commercially advertised vaccines, three for oral use and two for parenteral injection. Other groups received placebos or nothing at all. No clearcut evidence of protection against the cold was demonstrated in any group. Intranasal vaccination is of no value either.[141a]

134. Commission on Acute Respiratory Diseases: Endemic Exudative Pharyngitis and Tonsillitis; Etiology and Clinical Characteristics, J. A. M. A. **125**:1163-1169 (Aug. 26) 1944.

135. Holbrook, W. P.: The Army Air Forces Rheumatic Fever Control Program, J. A. M. A. **126**:84-87 (Sept. 9) 1944.

136. Coburn, A. F.: The Prevention of Respiratory Tract Bacterial Infections, J. A. M. A. **126**:88-92 (Sept. 9) 1944.

137. Freis, E. D.: The Treatment of Tonsillitis with Small Doses of Sulfonamides, J. A. M. A. **126**:93-94 (Sept. 9) 1944.

138. Cecil, R. L.; Plummer, N., and Smillie, W. G.: Sulfadiazine in the Treatment of the Common Cold, J. A. M. A. **124**:8-14 (Jan. 1) 1944.

139. Harris, T. N., and Stokes, J., Jr.: Air-Borne Cross Infection in the Case of the Common Cold: A Further Clinical Study of the Use of Glycol Vapors for Air Sterilization, Am. J. M. Sc. **206**:631-636 (Nov.) 1943.

140. Puck, T. T.; Robertson, O. H., and Lemon, H. M.: The Bactericidal Action of Propylene Glycol Vapor on Microorganisms Suspended in Air: II. The Influence of Various Factors on the Activity of the Vapor, J. Exper. Med. **78**:387-406 (Nov.) 1943.

140a. Schneiter, R.; Hollaender, A.; Camenita, B. H.; Kolb, R. W.; Fraser, H. F.; DuBuy, H. G.; Neal, P. A., and Rosenblum, H. B.: Effectiveness of Ultraviolet Irradiation of the Upper Air for the Control of Bacterial Air Contamination in Sleeping Quarters: Preliminary Report, Am. J. Hyg. **40**:136-153 (Sept.) 1944.

141. McGee, L. C.; Andes, J. E.; Plume, C. A.; Succasunna, N. J., and Hinton, S. H.: "Cold Vaccines" and the Incidence of the Common Cold, J. A. M. A. **124**:555-557 (Feb. 26) 1944.

141a. Cowan, D. W., and Diehl, H. S.: Ann. Otol., Rhin. & Laryng. **53**:286 (June) 1944.

The Psittacosis-Ornithosis Infections.—There is some question as to whether infectious agents of this group should be classified as filtrable viruses or placed in a group by themselves because of their visibility under the microscope in spite of being filtrable and of certain other characteristics.

An epizootic of a psittacosis-like infection among pigeons, and in 2 human beings, occurred.[142] The infection may be contracted by handling pigeon manure.[142a] It is not as yet known whether this virus, also called ornithosis virus, represents psittacosis virus as modified by existence in nonpsittacine hosts or whether it is different but closely related, as are, say, type I and type II pneumococci. Beck, Eaton and O'Donnell [143] admit that prolonged residence of a virus in different hosts may change its pathogenicity, but changes in antigenic structure, they believe, do not occur except as a result of an evolutionary process. According to them, the S-F virus of human pneumonitis and the virus of psittacosis are different from each other and from the viruses of ornithosis and mouse meningopneumonitis, which probably are identical.

California investigators [144] report clinical observations in 6 cases of infection with the S-F psittacosis-like strain of virus, 4 cases of ornithosis contracted from pigeons and 1 case of infection with mouse meningopneumonitis contracted in the laboratory. All the illnesses were so similar as to be indistinguishable clinically. Even the isolated viruses are so similar that it is necessary to correlate the pathogenicity of the virus for animals, the results of cross immunity tests and the epidemiologic history to differentiate them. The difficulties in differentiation are similar to those among the neurotropic viruses, as described on page 294. Incidentally, it is hoped that the authors' suggestion to adopt the term "pseudopsittacosis" will not be accepted. Different names indicating a relationship such as is inferred by the terms psittacosis and ornithosis or terms such as psittacosis type A and type B are much more desirable.

142. Smadel, J. E.; Wall, M. J., and Gregg, A.: An Outbreak of Psittacosis in Pigeons Involving the Production of Inclusion Bodies and Transfer of the Disease to Man, J. Exper. Med. **78**:189-203 (Sept.) 1943.

142a. Nauen, R., and Korns, R. F.: A Localized Epidemic of Acute Miliary Pneumonitis, Associated with the Handling of Pigeon Manure, Proc. Am. Pub. Health A., New York, Oct. 3, 1944.

143. Beck, M. D.; Eaton, M. D., and O'Donnell, R.: Further Laboratory Studies on the Classification of Psittacosis-Like Agents, J. Exper. Med. **79**:65-77 (Jan.) 1944.

144. Meiklejohn, G.; Beck, M. D., and Eaton, M. D.: Atypical Pneumonia Caused by Psittacosis-Like Viruses, J. Clin. Investigation **23**:167-175 (March) 1944.

The virus of mouse pneumonitis, which is also related to the psittacosis–ornithosis–lymphogranuloma venereum group, when injected into chickens, evokes an antiserum of good neutralizing titer.[145] The antiserum is efficient in the treatment of mice infected with the virus. The prediction in last year's review that the virus isolated from cats by Baker,[146] tentatively called ailourosis, which gives rise to elementary bodies, belongs in the psittacosis-ornithosis-etc. group was fulfilled by the work of Thomas and Kolb.[147] It is suggested that cats become infected by eating infected mice. It may be recalled that cases of human pneumonia were associated with the disease occurring concurrently in cats; this suggests contact infection. Cats are thus added to lengthen the list of sources of this large group of infectious agents.

The virus of mouse pneumonitis apparently resides in a latent state in many normal mice. It may be activated by injecting human serum into mice and can easily lead to false conclusions in studies on the cause of human pneumonias.[148]

Rake and his associates [149] suggest that all four of the viruses of the lymphogranuloma-psittacosis group produce a powerful toxin, which accounts for the early deaths in inoculated animals; death occurring later is caused by the infection itself. The validity of the suggestion is supported by the following tests: Since infections in animals caused by the viruses of lymphogranuloma venereum and mouse pneumonitis respond to sulfonamide compounds, treatment with such compounds was effective in saving animals that had survived the early effects of the toxin, which are not controlled by sulfonamide compounds. Furthermore,[150] sulfonamide compounds had no influence at all on infections caused by feline pneumonitis or meningopneumonitis. They demonstrate a toxin similar to bacterial endo-

145. Hilleman, M. R., and Gordon, F. B.: A Protective Antiserum Against Mouse Pneumonitis Virus, Science **98**:347-348 (Oct. 15) 1943.

146. Baker, J. A.: A Virus Causing Pneumonia in Cats and Producing Elementary Bodies, J. Exper. Med. **79**:159-172 (Feb.) 1944.

147. Thomas, L., and Kolb, E. M.: Relationship of the Virus of Cat Pneumonia (Baker) to the Psittacosis-Lymphogranuloma Group of Agents, Proc. Soc. Exper. Biol. & Med. **54**:172-174 (Nov.) 1943.

148. Thomas, L., and Kolb, E. M.: Activation of Latent Mouse Pneumonitis Virus by Human Serum, Proc. Soc. Exper. Biol. & Med. **55**:1-4 (Jan.) 1944.

149. Rake, G., and Jones, H. P.: Studies on Lymphogranuloma Venereum: II. Association of Specific Toxins with Agents of the Lymphogranuloma-Psittacosis Group, J. Exper. Med. **79**:463-485 (May) 1944.

150. Rake, G., and Hamre, D. M.: Action of Sulfonamides on Toxins of Agents of the Lymphogranuloma-Psittacosis Group, Proc. Soc. Exper. Biol. & Med. **55**: 90-91 (Feb.) 1944.

toxins from the viruses of lymphogranuloma venereum, mouse meningomeningitis, mouse pneumonitis and feline pneumonitis. This is still another factor which differentiates this group of infectious agents from true filtrable viruses and justifies their inclusion as a separate group. Weak antitoxin can be prepared with these antigens, and serum from patients convalescent from lymphogranuloma venereum is also antitoxic.

DISEASES PROBABLY CAUSED BY VIRUSES

Virus Pneumonia; Nonbacterial Pneumonia.—Numerous clinical and etiologic studies [151] on the primary pneumonias of unknown cause signify the continued wide interest in this group of diseases. Although unrecognized or disregarded only a few years ago, they are, numerically at least, the most important forms of pneumonia in the armed forces at present.[152] Actually, little of importance has been added to the knowledge already at hand.

It is unfortunate that the syndrome is now commonly called "atypical pneumonia." One may as well call lymphocytic choriomeningitis "atypical meningitis" in comparison with meningococcic meningitis. The syndrome is certainly typical in itself, and since it comprises between 85 and 90 per cent of all attacks of pneumonia at certain times,[153] why should *it* not be regarded as "typical" pneumonia? The adjective typical was originally applied to the classic pneumococcic lobar pneumonia when interest in that disease was at its height. Any other pneumonia, primary or not, bacterial or nonbacterial, which did not conform clinically to lobar pneumonia was called atypical. Therefore, if the recommendation of the Surgeon General of the Army is accepted, as it appears to be, the whole name "primary atypical pneumonia, etiology unknown" must be used to differentiate the disease from atypical pneumonias caused by known agents. Otherwise the term atypical is ambiguous. Evidence is accumulating [154] that a virus infectious for cotton rats may cause a certain proportion of the disease. If this is the case, the simple term "virus" pneumonia may be justified after all. Anyway the term is more definitive. It is questionable if the word pneumonia should be used at all, since in the majority of infections caused by the same agent the lungs are not involved.

It is generally agreed that the disease in most instances is primarily one of the respiratory tract and that in only a small proportion of cases can the cause be determined. Evidence is accumulating to support the view I gave in 1938, that the attacks with involvement of the lungs are only the severe forms of a common, mild epidemic infection of the respiratory tract. In Favour's experience,[155] for example, 231 of 300 persons directly exposed to the infection became sick; of these 12 per cent had pneumonia, 71 per cent had tracheobronchitis and the rest had only fever or fatigue. In an Army post the incidence of pneumonic attacks was parallel with the incidence of minor infections of the respiratory tract.[153]

In what seems to be a different type of disease, including instances of infection of known cause, discussed on page 299, severe attacks are not accompanied by a number of mild grades of infection. The disease seems to be a systemic one in which the lungs are usually involved. I have published evidence [156] that a severe form of the disease may occur without pneumonia, and similar cases were observed by Owen.[151b] If this actually is the case, the use of the word pneumonia designates only those attacks of an infectious disease in which the lungs are involved and disregards the others. It will be better, eventually, when the causes are discovered, to coin and apply names to include all gradations of severity of each established entity.

An unusual form of pneumonitis appeared in Louisiana.[156a]

151. (*a*) Dingle, J. H.; Abernathy, T. J.; Badger, G. F.; Buddingh, G. J.; Feller, A. E.; Langmuir, A. D.; Ruegsegger, J. M., and Wood, W. B.: Primary Atypical Pneumonia, Etiology Unknown: I., Am. J. Hyg. **39**:67-128 (Jan.) 1944; II., ibid. **39**:197-268 (March) 944; III, ibid. **39**:269-336 (May) 1944. (*b*) Owen, C. A.: Primary Atypical Pneumonia: An Analysis of Seven Hundred and Thirty-Eight Cases Occurring During 1942 at Scott Field, Ill., Arch. Int. Med. **73**:217-231 (March) 1944. (*c*) Van Ravenswaay, A. C.; Erickson, G. C.; Reh, E. P.; Siekierski, J. M.; Pottash, R. C., and Gumbiner, B.: Clinical Aspects of Primary Atypical Pneumonia, J. A. M. A. **124**:1-6 (Jan. 1) 1944.

152. Dingle, J. H.: Primary Atypical Pneumonia, Am. J. Pub. Health **34**:347-357 (April) 1944.

153. Langmuir, A. D.: Epidemiology of Atypical Pneumonia and Acute Respiratory Disease at Fort Bragg, North Carolina, Am. J. Pub. Health **34**:335-346 (April) 1944.

154. Eaton, M. D.; Meiklejohn, G., and Van Herick, W.: Studies on the Etiology of Primary Atypical Pneumonia: A Filtrable Agent Transmissible to Cotton Rats, Hamsters and Chick Embryos, J. Exper. Med. **79**:649-668 (June) 1944.

155. Favour, C. B.: Infections Associated with an Epidemic of Primary Interstitial Pneumonia, New England J. Med. **230**:537-542 (May 4) 1944.

156. Reimann, H. A.: Primary Atypical Pneumonias of Unknown Cause: "Virus" of "Viral" Pneumonias; Case Report of a Similar Disease Without Pneumonia, J. Michigan M. Soc. **43**:147-150 (Feb.) 1944.

156a. Olson, B. J., and Treuting, W. L.: An Epidemic of a severe Pneumonitis in the Bayou Region of Louisiana, Pub. Health Rep. **59**:1299-1311 (Oct. 9) 1944.

The "viral" pneumonias in my experience have been much less prevalent in the current season than in the year before. Several cases with complicating encephalitis [157] or meningomyelitis [158] are reported, which bears out the suggestion made in my first paper in 1938 that the infectious agent may at times be neurotropic as well as pneumonotropic. Pericarditis is also recorded.[159] Studies from one military source [151b] reveal a number of other complications or sequels, such as pleural effusion, empyema and bronchiectasis, while in observations from another source [152] complications were as rare as they are generally believed to be. Certain forms of the infection are not highly contagious,[152] and in an experimental study [160] nasopharyngeal washings from 12 patients were injected intranasally into 5 volunteers without transmitting the disease. In other experiments,[160a] however, the disease was transmitted to 10 of 12 volunteers by spraying nasal washings from patients into the nose and throat.

The development of a cold agglutinin during the disease has provoked much study. The test for cold agglutination was positive in 90 per cent of a group of cases in England [161] in 1942-1943 and in 25 to 50 per cent of cases at Fort Bragg.[162] Meiklejohn [162] confirmed previous reports as to the specificity of the test in certain groups of cases. It was positive in 80 per cent of his cases and reached its highest titer in the second or third week. Unfortunately, the reaction becomes positive too late to be of value in early diagnosis. The test gave negative results in other infections of the respiratory tract and, as in my experience, in 2 cases of the sporadic form of psittacosis-like disease. Two British Army authors,[163] apparently unaware of previous work on the subject and on the viral pneumonias in general, report "autohemagglutinin" in each of 54 cases. Many of their patients also had malaria, which suggests that the complication of two diseases may confuse the results. Parekh [164] has apparently been similarly confused and ascribes autoagglutination in the cold to sulfapyridine therapy in cases of infection of the respiratory tract. Dameshek [165] reports the development of a hemolytic crisis with jaundice and with cold agglutination in the blood in 2 probable cases of viral pneumonia in which excessive therapy with sulfonamide compounds was used. The question may arise as to whether or not chemotherapy aggravates the reaction. Others [166] noted acrocyanosis and a cold agglutinin in a patient one month after probable viral pneumonia.

Canadian observers [166a] conclude that the cold agglutination test is of no value in diagnosis. Cold agglutinins are present or absent in pneumococcic or viral pneumonias and in other diseases of the respiratory tract.

Etiology.—Further evidence is published [154] of the etiologic relationship of the previously reported "cotton rat virus" to the disease in studies which carefully avoid confusion with viruses latent in the rats themselves. The virus is of low virulence, is relatively labile and has a longer incubation period than other agents which cause pneumonia in cotton rats and hamsters. The virus is specifically neutralized by serum from patients who recovered from the disease. The chances of isolating the virus are increased by inoculating sputum obtained early in the course. The virus is usually obtained from patients who acquire a cold agglutinin in their blood. The same virus evidently also causes mild disease without pneumonia.

157. Perrone, H., and Wright, M.: A Fatal Case of Atypical Pneumonia with Encephalitis, Brit. M. J. **3**:63-65 (July 17) 1943. Hein, G. E., in discussion on Primary Atypical Pneumonia, Lancet **1**:431-432 (April 3) 1943.

158. Sheppe, W. M.; Osterman, A. L.; Ahroon, C. R., and Zuflacht, J. J.: Meningomyelitis: A Complication of Atypical Pneumonia, J. A. M. A. **122**: 1245-1246 (Aug. 28) 1943.

159. Finkelstein, D., and Klainer, M. J.: Pericarditis Associated with Primary Atypical Pneumonia, Am. Heart J. **28**:385-394 (Sept.) 1944.

160. Vance, D. H., and Mason, H. C.: Inability to Pass Primary Atypical Pneumonia to Human Volunteers, Science **98**:412-413 (Nov. 5) 1943.

160a. Conscientious Objectors Contract Disease to Help Army Fight Infection, J. A. M. A. **125**:636 (July 1) 1944.

161. Turner, J. C., and Jackson, E. B.: Serologic Specificity of Autoantibody in Atypical Pneumonia, Brit. J. Exper. Path. **24**:121-126 (June) 1943.

162. Meiklejohn, G.: The Cold Agglutination Test in the Diagnosis of Primary Atypical Pneumonia, Proc. Soc. Exper. Biol. & Med. **54**:181-184 (Nov.) 1943.

163. Shone, S., and Passmore, R.: Pneumonitis Associated with Autohemagglutination, Lancet **2**:445-446 (Oct. 9) 1943.

164. Parekh, J. G.: Phenomenon of Autoagglutination in Man After Sulfapyridine, Indian M. Gaz. **78**: 527-531 (Nov.) 1943.

165. Dameshek, W.: Cold Agglutination in Acute Hemolytic Reactions in Association with Sulfonamide Medication and Infection, J. A. M. A. **123**:77-80 (Sept. 11) 1943.

166. Helwig, F. C., and Freis, E. D.: Cold Autohemagglutinins Following Atypical Pneumonia Producing the Clinical Picture of Acrocyanosis, J. A. M. A. **123**:626-628 (Nov. 6) 1943.

166a. Rich, C. B.; Rae, M. V., and McGoey, C. J.: Cold Agglutinins and the Pneumonias, Canad. M. A. J. **51**:239-240 (Sept.) 1944.

The frequent presence of nonhemolytic streptococci in large numbers in patients with viral pneumonia led to suspicion of their participation in the cause of viral pneumonias. Most observers, including myself, regard them as commensals. In one study [167] streptococci of a certain strain isolated from the lung in a fatal case were agglutinated by the convalescent serum of many patients who had had the disease, but not by serum taken during the acute phase or from patients who had had other infections, including psittacosis and influenza A. The results of the tests correlated in many instances, but not in all, with the results of the cold agglutinin test.

Streptococci and the serologic response to their presence may cause as much confusion in this field as they did in the rheumatic diseases, or one may recall the confusion resulting from the presence of Haemophilus influenzae of Pfeiffer in cases of influenza and of Salmonella cholerae suis in hog cholera, neither of which caused the respective diseases.

Treatment.—Correll and Cowan [168] advance evidence to show that roentgenotherapy reduces the duration of the disease and hastens the disappearance of abnormal roentgenographic shadows in the lung. If further work confirms its effect in shortening the disease, the treatment is of value, but there is no reason to be concerned about the residual shadows which in almost all cases vanish harmlessly if left alone. It is disappointing, in spite of all that has previously been written to the contrary, that the sulfonamide compounds are still widely used or advocated to be used in treatment or prevention, "just in case" the pneumonia may be mistaken for one of pneumococcic origin.

Smallpox Pneumonia (?).—In a small outbreak of smallpox, the signs and symptoms characteristic of viral pneumonia developed in 7 persons between the eleventh and the fourteenth day after contact with the source of infection in a patient.[168a] It is inferred that the pulmonary reaction was caused by the virus of smallpox.

Epidemic Diarrhea, Nausea and Vomiting.—Probably because this disease is usually mild and of short duration and because its cause is unknown, little attention has been given to it in spite of the appearance of a number of publications concerning it during the past twenty years. There is evidence,[169] however, that the infection was widespread [170] or even pandemic in the late months of 1943. When it occurs it is often regarded as a minor ailment in the nature of indigestion, "intestinal influenza" or "water sickness" and usually disregarded in the press of other matters. In isolated cases, pain in the abdomen, nausea, vomiting, fever and leukocytosis may suggest acute appendicitis, just as occurred after the outbreak of amebic dysentery during the Century of Progress celebration in Chicago. Occasionally sudden outbreaks involving family, school, barrack or hospital groups are suspected of being caused by food poisoning. They also may be mistaken for epidemics of bacillary dysentery, especially in regions where it is likely to occur. I made numerous unsuccessful attempts to recover dysentery bacilli in small outbreaks of mild diarrheal disease among occidentals in China in 1928, and at the time I suspected some unknown nonbacterial infectious agent to be the cause. It is possible that many infections diagnosed as bacillary dysentery in the armed forces who are located in endemic areas or elsewhere belong to the syndrome in question. To illustrate the point, reference may be made here to similar diagnostic confusion which occurred in the Italian campaign: Many soldiers believed to have had malaria, because of its endemicity, actually had sandfly fever.

In various epidemics of nausea, vomiting and diarrhea thus far recorded, slight differences in clinical behavior have been recorded. For example, in some reported cases nausea and vomiting predominated, and in others, as in ours, diarrhea was the outstanding symptom. Perhaps slightly different but related infectious agents account for these differences, but it would seem that most of the infections described can be grouped as a syndrome.

It is unknown at present whether or not the disease is related to the severe epidemic diarrheal disease of unknown cause which affects newborn infants in nurseries.

Etiology.—None of the bacteria ordinarily associated with enteritis has been incriminated as

167. Thomas, L.; Mirick, G. S.; Curnen, E. C.; Ziegler, J. E., and Horsfall, F. L.: Serological Reactions with an Indifferent Streptococcus in Primary Atypical Pneumonia, Science **98**:566-568 (Dec. 24) 1943.

168. Correll, H. L., and Cowan, I. I.: Primary Atypical Pneumonia: Analysis of Therapeutic Results in 155 Cases, U. S. Nav. M. Bull. **41**:980-987 (July) 1943.

168a. Howat, H. T., and Arnott, W. M.: Outbreak of Pneumonia in Smallpox Contacts, Lancet **2**:312 (Sept. 2) 1944.

169. Reimann, H. A.; Price, A. H., and Hodges, J. H.: Epidemic Diarrhea, Nausea and Vomiting of Unknown Cause, J. A. M. A., to be published.

170. Gauss, H.: Seasonal Gastroenteritis in Colorado, Am. J. Digest. Dis. **11**:40-43 (Feb.) 1944. Korns, R. F.: An Unusual Waterborne Outbreak of Gastroenteritis, J. Bact. **47**:528 (June) 1944.

the cause. Poisoning by infected food or water has been eliminated. The infection appears at present to be air borne. As in the case of the nonbacterial or "viral" pneumonias, therefore, a filtrable virus has been suspected. Europeans have suggested it to be a neurotropic one giving rise to secondary gastrointestinal symptoms, even in the absence of other neurologic signs or symptoms. Should a filtrable agent or agents be proved to be a cause of the syndrome, a field for investigation as great and as important as that for the viral pneumonias will be opened.

Curiously, until recently no virus was known to be especially enterotropic, although the discovery of such a one may have been predicted. Silva [171] isolated a filtrable virus causing enteritis in cats, and Baker [172] reports one which is apparently both pneumonotropic and enterotropic in calves, but the first intimation that a virus may attack the human intestinal tract comes from experiments performed by Light and Hodes.[173] These investigators report the transmission of a diarrheal disease to calves regularly by inoculation with a filtrable infectious agent obtained from the stools of infants with severe diarrhea of the newborn. One attack conferred immunity to reinoculation and specific protection tests seemed to verify their belief that they dealt with the cause of the disease. Their results, however, need confirmation, since calves are notoriously subject to other diarrheal diseases, and according to their statement the infectious agent survives boiling (!) for five minutes.

In our own experiments [174] filtered material from 8 adults inoculated intranasally into as many calves caused no evidence of disease. We were also unable to detect any infectious agent by injecting filtrates of stools by various routes into mice or in eggs.

Epidemic Hepatitis.—Pathologic changes in the liver were studied by aspiration biopsy [175] and at necropsy [176] on patients with infectious jaundice who died from other causes. The changes found were not specific. There were degeneration, ulceration, necrosis and autolysis of the liver cells, especially in the center of the lobules, and leukocytic and histiocytic proliferation of the periportal tissues. The process terminates in complete restoration, in acute or subacute necrosis ("atrophy"), in mild fibrosis or in cirrhosis. According to Lucké,[176] there is little doubt that idiopathic yellow atrophy in some cases represents the end stage of fatal epidemic hepatitis. No evidence was found to substantiate the old idea of catarrh of the duct and obstruction as the cause of jaundice.

Jaundice has been induced in 3 volunteers by nasal instillation of nasal washings from patients with jaundice following vaccination for yellow fever [177] and by subcutaneous inoculation of serum from another patient.[178] The causative agent appears to survive and multiply in chick embryo cultures. The inference is that a filtrable agent is responsible. Although it seems so, it is not proved that the induced disease is identical with the syndrome called infectious jaundice.

In other studies,[179] the disease was transmitted to 6 patients with rheumatoid arthritis by the oral administration or nasal spray of material prepared from feces or serum of patients with infectious hepatitis. The resulting jaundice relieved the arthritic pains in all 6 volunteers. Extensive reports [180] of official investigations of hepatitis following vaccination against yellow fever were published.

In serum from patients with acute hepatitis resulting from vaccination against yellow fever,

171. Silva, M.: Mal epizoótico de gato doméstico no Ceará, Hospital, Rio de Janeiro **18**:1015-1018 (Dec.) 1940.

172. Baker, J. A.: A Filtrable Virus Causing Enteritis and Pneumonia in Calves, J. Exper. Med. **78**: 435-445 (Dec.) 1943.

173. Light, J. S., and Hodes, H. L.: Studies in Epidemic Diarrhea of the New-Born: Isolation of a Filtrable Agent Causing Diarrhea in Calves, Am. J. Pub. Health **33**:1451-1454 (Dec.) 1943.

174. Reimann, H. A.; Price, A. H., and Hodges, J. H.: Negative Results in Studies of Epidemic Diarrhea, Nausea and Vomiting of Unknown Cause, Proc. Soc. Exper. Biol. & Med. **55**:235-236 (April) 1944.

175. Siegmund, H.: Pathologic Anatomy of Epidemic Hepatitis, München. med. Wchnschr. **89**:463-468 (May 22) 1942. Dible, J. H.; McMichael, J., and Sherlock, S. P. V.: Pathology of Acute Hepatitis, Lancet **2**:402-407 (Oct. 2) 1943.

176. Lucké, B.: The Pathology of Fatal Epidemic Hepatitis, Am. J. Path. **20**:471-527 (May) 1944; The Structure of the Liver After Recovery from Epidemic Hepatitis, ibid. **20**:595-611 (May) 1944.

177. Findlay, G. M., and Martin, N. H.: Jaundice Following Yellow Fever Immunization: Transmission by Intranasal Instillation, Lancet **1**:678 (May 29) 1943.

178. MacCallum, F. O., and Bauer, D. J.: Hemologous Serum Jaundice: Transmission Experiments with Human Volunteers, Lancet **1**:622-627 (May 13) 1944.

179. MacCallum, F. O., and Bradley, W. H.: Transmission of Infectious Hepatitis in Human Volunteers: Effect on Rheumatoid Arthritis, Lancet **2**:229 (Aug. 12) 1944.

180. Sawyer, W. A.; Meyer, K. F.; Eaton, M. D.; Bauer, J. H.; Putnam, P., and Schwentker, F. F.: Jaundice in Army Personnel in the Western Region of the United States and Its Relation to Vaccination Against Yellow Fever, Am. J. Hyg. **39**:337-430 (May) 1944; **40**:35-107 (July) 1944. Findlay, G. M.; Martin, N. H., and Mitchell, J. B.: Hepatitis After Yellow Fever Inoculation: Relation to Infective Hepatitis, Clinical and Pathological Fndings, Lancet **2**:301-307 (Sept. 2); 340-344 (Sept. 9) 1944.

the existence of an "antigen" was demonstrated [181] during the acute phase of the disease, which precipitates an antibody in serum obtained in convalescence. The reaction is similar to those previously reported in cases of yellow fever itself and was thought to be due to injury of the liver. The test, unless it can be improved, is not satisfactory for the diagnosis of hepatitis. Further studies indicate that complement fixation with human liver and agglutination of sheep cells have frequently been associated with acute hepatitis. This suggests that a single antigen-antibody system accounts for both reactions. The heterogenetic antibody is different from other human heteroantibodies. The occurrence of urticaria in certain cases of acute hepatitis suggests hypersensitivity and the action of the antibody-antigen union in the body.

Infectious Mononucleosis.—British investigators [182] made a survey of an outbreak of infectious mononucleosis in a military hospital and in the adjacent community. After the first few cases were recognized, a study was made of all other patients and of the staff, comprising 296 persons in all. Of these, 290 gave evidence of having the infection, 125 in clinical form and 165 without clinical manifestations. Of special interest is the last group of 165 apparently healthy persons for whom the diagnosis was established only by the characteristic leukocytic changes and by the heterophile antibody test. The study illustrates how widespread this disease may be and shows that the majority of patients with it are actually symptomless and would never be recognized as having it without special tests. Even clinically manifest forms are apt to be misdiagnosed for gastroenteritis or grip if the disease is not in mind or if appropriate tests are not made.

Necropsy in one of the unusual fatal cases of infectious mononucleosis is reported.[183] Attempts to transmit infectious mononucleosis to human volunteers and to animals by Julianelle and his associates [184] were unsuccessful. A filtrable virus is suspected to be the cause.

Sandfly Fever.—Phlebotomus (or flebotomus, Pappataci or sandfly) fever is a common exotic disease which has affected large numbers of the armed forces. Clinically it resembles grip and is also called three day fever.[184a]

Acute Infectious Lymphocytosis.—Under this heading Smith [185] describes several cases of a condition which could easily be confused with infectious mononucleosis or leukemia except for the mildness of the disease and the absence of splenomegaly, of enlargement of the lymph nodes and of heterophile agglutinin in the blood. There is usually evidence of an associated infection of the upper respiratory tract. Characteristically there is hyperleukocytosis with a preponderance of normal lymphocytes.

Because of the circumstances described and of the peculiar changes in the excised lymph nodes the author believes the disease to be a specific entity probably caused by a virus related to infection of the respiratory tract. On the other hand, it may simply represent an unusual hematologic response to a banal infection, analogous to the so-called "leukemoid" reaction occasionally observed. There is no need to regard the disease as one "of recent origin" just because it has only recently been described.

A peculiar disease at first confused with acute appendicitis was observed [186] in 50 patients in a six month period at an army post. Thirteen patients were inadvertently operated on. The onset was sudden, with knifelike pains in the lower part of the abdomen, nausea and vomiting. The face was flushed, the conjunctivas injected and the soft palate edematous. The duration of the disease was from one to ten days. There was no fever, and the leukocytes were undisturbed. In the absence of a discoverable cause, a filtrable virus attacking the nerve roots was suspected.

Several reports [187] published during the year from widely separated places describe a peculiar severe disease characterized by eruptions in the mouth, urethra and conjunctivas. The disease was probably the same in each instance and occurred in young adults. The cause is unknown.

181. Eaton, M. D.; Murphy, W. D., and Hanford, V. L.: Heterogenetic Antibodies in Acute Hepatitis, J. Exper. Med. **79**:539-557 (May) 1944.

182. Halcrow, J. P. A.; Owen, L. M., and Rodger, N. O.: Infectious Mononucleosis with an Account of an Epidemic in an E. M. S. Hospital, Brit. M. J. **2**: 443-447 (Oct. 9) 1943.

183. Ziegler, E. E.: Infectious Mononucleosis: Report of Fatal Case with Autopsy, Arch. Path. **37**:196-201 (March) 1944.

184. Julianelle, L. A.; Bierbaum, O. S., and Moore, C. V.: Studies on Infectious Mononucleosis, Ann. Int. Med. **20**:281-291 (Feb.) 1944.

184a. Sabin, A. B.; Philip, C. B., and Paul, J. R.: Phlebotomus (Pappataci or Sandfly Fever), J. A. M. A. **125**:603-606 (July 1); 693-699 (July 8) 1944.

185. Smith, C. H.: Acute Infectious Lymphocytosis: A Specific Infection; Report of Four Cases Showing Its Communicability, J. A. M. A. **125**:342-349 (June 2) 1944.

186. Butsch, W. L., and Harberson, J. C.: Acute Virus Infection with Nerve Root Involvement Simulating Appendicitis, J. A. M. A. **123**:405-407 (Oct. 16) 1943.

187. Murphy, R. C.: Eruptive Fever, Involving Mouth and Eyes (Stevens-Johnson's Disease): Report of a Case, New England J. Med. **230**:69-71 (Jan. 20) 1944. Langille, J. A.: Acute Membranous Stomatitis and Conjunctivitis (Report of 3 Cases), Canad. M. A. J. **50**:141-143 (Feb.) 1944.

RHEUMATOID ARTHRITIS AND RHEUMATIC FEVER

Using strict clinical criteria for the diagnosis of rheumatoid arthritis in 61 patients who died and were studied at necropsy, Fingerman and Andrus [188] found lesions indistinguishable from those of rheumatic heart disease in 19; only 3 had splenomegaly and anemia (Felty's syndrome); amyloidosis was present in 13, and glomerulitis was noted in 8. Either the patients with rheumatoid arthritis and rheumatoid-fever-like lesions had had rheumatic fever before, or, as many have suggested throughout the years, the two diseases are different manifestations of the same infection, or the lesions are nonspecific and may arise from various causes.

Although Aschoff bodies are generally regarded as strictly specific for rheumatic fever, Rich and Gregory [189] caused similar lesions in the hearts of rabbits by injecting horse serum intravenously. Granting that these lesions are not the same as the ones discovered in 1924 by Miller in "normal" rabbits, the observations suggest that the lesions of rheumatic fever may be focal reactions of the anaphylactic type. If this is the case they can hardly be regarded as specific for rheumatic fever any longer. In another study Rich and Gregory [190] call attention to the similarity of the lesions in rheumatic pneumonitis and the pneumonitis caused by hypersensitivity to sulfonamide compounds as providing additional evidence of the anaphylactic nature of the lesions of acute rheumatic fever.

In Selye's paper [191] the issue is even more complicated. Selye and his associates also produced Aschoff bodies and polyarthritis in rats, but with massive doses of desoxycorticosterone acetate, particularly in rats whose thyroid and adrenal glands had been removed. They interpret the results as indicating that hyperactivity of the adrenal cortex plays an important role in causing both rheumatic fever and rheumatoid arthritis. For good measure, they include hypertrophic arthritis, periarteritis nodosa and scleroderma in the picture, and quote over 200 references to support their views. They do "not try to differentiate sharply between the various types of chronic arthritis," which indeed annoys those who do. While it is granted from the data that overdosage of desoxycorticosterone acetate does cause a form of arthritis and certain histologic changes in the tissues of rats, it seems premature and unsafe to conclude that acute rheumatic fever or rheumatoid arthritis is caused by hormonal disturbance.

After a lapse of several years Loewenstein [192] resurrects his unfounded notion that rheumatic fever is caused by tubercle bacilli. It is surprising to find so uncritical an article as his in as good a journal as the *American Review of Tuberculosis*. He even advises treatment with tuberculin! According to him Aschoff's nodules occur in tuberculosis. From what has been mentioned before in this review the Aschoff nodule is indeed ubiquitous.

In the report of a study [193] of 8 cases of rheumatic pneumonia it is suggested that the granulomatous lesions in the lung which seem to be the equivalent of Aschoff bodies in the heart be called "Masson bodies."

According to Coburn, [194] massive doses of sodium salicylate (10 Gm. daily) apparently prevented valvular heart disease in 38 rheumatic patients while in 21 of 63 patients who received small doses heart disease developed. A plasma level of 350 micrograms of salicylate per cubic centimeter, he states, is necessary to suppress the rheumatic reaction; plasma levels below 200 micrograms may only relieve symptoms without controlling the inflammatory process. If this is true, the view that the exudative reaction can be controlled while the proliferative changes of rheumatic fever cannot will have to be revised.

In further discussion on hereditary susceptibility to rheumatic fever, Wilson [195] points out that in a series of rheumatic families the distribution of cases followed the general laws of inheritance, the frequency being consistent with recessive mendelian inheritance. For example, if both parents are rheumatic nearly every child will be

188. Fingerman, D. L., and Andrus, F. C.: Visceral Lesions Associated with Rheumatoid Arthritis, Ann. Rheumat. Dis. **3**:168-180 (May) 1943.

189. Rich, A. R., and Gregory, J. E.: Experimental Evidence that Lesions with the Basic Characteristics of Rheumatic Carditis Can Result from Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **73**:239-264 (Oct.) 1943.

190. Rich, A. R., and Gregory, J. E.: Anaphylactic Nature of Rheumatic Pneumonia, Bull. Johns Hopkins Hosp. **73**:465-478 (Dec.) 1943.

191. Selye, H.; Sylvester, O.; Hall, C. E., and Leblond, C. P.: Hormonal Production of Arthritis, J. A. M. A. **124**:201-207 (Jan. 22) 1944.

192. Loewenstein, E.: Rheumatic Diseases and Tuberculosis, Am. Rev. Tuberc. **49**:58-77 (Jan.) 1944.

193. Neuberger, K. T.; Geever, E. F., and Rutledge, E. K.: Rheumatic Pneumonia, Arch. Path. **37**:1-15 (Jan.) 1944.

194. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever: Rational Technic, Bull. Johns Hopkins Hosp. **73**:435-464 (Dec.) 1943.

195. Wilson, M. G.: Hereditary Susceptibility in Rheumatic Fever: The Potential Rheumatic Family, J. A. M. A. **124**:1188-1189 (April 22) 1944. Wilson, M. G.; Schweitzer, M. D., and Lubschez, R.: The Familial Epidemiology of Rheumatic Fever: Genetic and Epidemiologic Studies, J. Pediat. **22**:468-492 (April); 581-611 (May) 1943.

susceptible; if one parent is rheumatic and the other a "rheumatic carrier" each child has a 50 per cent chance to be susceptible. If neither parent is rheumatic but if both are carriers (rheumatic fever present in the immediate families) each child has a 25 per cent chance. The obvious hereditary nature of the malady suggests public health control, as in tuberculosis. On the other hand, rheumatic fever was not found to exhibit the usual characteristics of a communicable disease nor the operation of any specific bacterial agent. No evidence supports the view that infection is acquired by contact, and hemolytic streptococci would seem to be no more likely to precipitate an attack than any other micro-organism. According to this view, the rheumatic process may be the result of the response of susceptible tissues to specific or nonspecific agents, which need not necessarily be bacterial in nature.

Granuloma inguinale may manifest itself as arthritis and give rise to diagnostic confusion unless the causative agent is recognized.[196]

Rickettsial Diseases.—Dyer [197] summarizes the current knowledge of the rickettsial diseases but curiously fails to include "Bullis fever," a disease recently discovered by Woodland [198] among troops in Texas. According to Dyer the rickettsial diseases of man may be classified into four groups:

Typhus	Rocky Mountain Spotted Fever
Epidemic (louse borne)	Boutonneuse fever
Endemic (murine)	São Paulo "typhus"
	Tobia fever
	Kenya "typhus"
	Indian tick "typhus"
	South African tick bite fever
Q Fever	**Tsutsugamushi**
Australian Q fever	Scrub "typhus"
American Q fever	Mite-borne diseases

The place of Bullis fever in the classification is as yet uncertain. It may be included with one of the four, probably with Rocky Mountain spotted fever, or may represent a distinct fifth type. The disease is apparently transmitted by ticks and resembles mild typhus clinically, except for lymphadenopathy and absence of the Weil-Felix reaction of the serum. Livesay and Pollard [199] found rickettsia-like bodies in guinea pigs inoculated with blood which are probably the causative agents.

Tsutsugamushi is described in detail by observers [200] in the South Pacific area. It is transmitted by a mite in wooded regions of heavy rainfall. Clinically the disease resembles other rickettsial diseases except for a primary ulcer, local or general adenopathy and an agglutin in the serum for Bacillus proteus OXK.

Colorado tick fever was finally proved to be a separate entity and not a mild form of Rocky Mountain spotted fever.[200a] It is transmitted by ticks, but it is uncertain if rickettsias are the cause, although basophilic cytoplasmic bodies are occasionally found in lymphocytes of infected animals.

Bengston [201] describes more fully the details of a reliable complement fixation test for the diagnosis of rickettsial diseases. According to others,[202] boutonneuse fever can be differentiated from Rocky Mountain spotted fever by the complement fixation test, even though they are antigenically related.

Topping [203] reports further success in treating guinea pigs and monkeys infected with Rocky Mountain spotted fever with serum. Immune serum given soon after inoculation suppressed the disease. "Benefit could be demonstrated" even if serum was given as late as the second day of fever. Fifty-two patients with the disease were treated, but the results are said not to be conclusive, even though only 2 deaths were recorded (3.8 per cent, as compared with the expected rate of 18.8 per cent). Serum to be of value should be given before the second day of disease, and with human beings it may be difficult except in epidemics to establish diagnosis

196. Scott, R. B.; Lyford, J. L., and Johnson, R. W.: Granuloma Inguinale as a Cause of Arthritis and Osteomyelitis, Bull. Johns Hopkins Hosp. **74**:213-217 (March) 1944.

197. Dyer, R. E.: The Rickettsial Diseases, J. A. M. A. **124**:1165-1172 (April 22) 1944.

198. Woodland, J. C.; McDowell, M. M., and Richards, J. T.: Bullis Fever (Lone Star Fever—Tick Fever), J. A. M. A. **125**:1156-1160 (Aug. 21) 1943.

199. Livesay, H. R., and Pollard, M.: Laboratory Report on a Clinical Syndrome Referred to as "Bullis Fever," Am. J. Trop. Med. **23**:475-480 (Nov.) 1943.

200. Ahlm, C. E., and Lipshutz, J.: Tsutsugamushi Fever in the Southwest Pacific Theater, J. A. M. A. **124**:1095-1100 (April 15) 1944.

200a. Florió, L.; Stewart, M. O., and Mugrage, E. R.: The Experimental Transmission of Colorado Tick Fever, J. Exper. Med. **80**:165-196 (Sept.) 1944.

201. Bengston, I. A.: Complement Fixation in the Rickettsial Diseases—Technique of the Test, Pub. Health Rep. **59**:402-405 (March 24) 1944.

202. Plotz, H.; Reagan, R. L., and Wertman, K.: Differentiation Between Fievre Boutonneuse and Rocky Mountain Spotted Fever by Means of Complement Fixation, Proc. Soc. Exper. Biol. & Med. **55**:173-176 (March) 1944.

203. Topping, N. H.: Rocky Mountain Spotted Fever: Further Experience in the Therapeutic Use of Immune Rabbit Serum, Pub. Health Rep. **58**:757-775 (May 14) 1943.

so early, since the eruption usually appears after that time.

In a clinical report,[204] good results are said to follow injections of combined (!) solutions of metaphen and neoarsphenamine, which are supposedly synergistic. The method hardly deserves trial. The author in addition raises the needless alarm of a spread of the disease. There is no reason to suspect that it is spreading. Objection is also made to his recommendation of cauterizing the site of the tick bite, which is unnecessary and even dangerous.

According to 2 reports, typhus was successfully treated. In one [204a] antityphus horse serum is said to reduce the mortality rate from about 11 per cent to 4 per cent. The paper is unconvincing. In the other,[204b] paraaminobenzoic acid was given in doses of 4 to 8 Gm. initially and 2 Gm. every two hours thereafter for several days, so that the level in the blood rested between 10 and 20 mg. per hundred cubic centimeters. The drug appeared to shorten the duration of the disease from an average of thirty-two days in untreated patients to twenty-one days, and to lessen the severity of the disease.

The work of Ding, in Germany, testing the prophylactic value of typhus vaccines is discussed in the *Lancet* of December 18. Vaccines prepared from louse gut, egg yolk and rabbit and dog lungs were all effective. No deaths occurred in vaccinated persons, as compared with a fatality rate of 20 to 30 per cent in unvaccinated persons. The incidence of the disease was not affected, but its severity was lessened.

Apparently of much greater effectiveness and reliability in the control of epidemic typhus are methods of louse disinfestation by insecticides or repellents, such as DDT powder, as used among the military and civil populations during the Italian campaign. Although the substance (dichlorodiphenyltrichloroethane) was synethesized in 1874, its powerful insecticidal property was not recognized until several years ago, by Muller, a Swiss scientist.

Experiments made in Mexico [205] suggest that cats may serve as reservoirs of endemic typhus. Natural infection probably occurs through flea bites or by ingestion of infected material. The rickettsias of endemic typhus were found for the first time in wild rats in California.[206]

Malaria.—Boyd [207] discusses the current information concerning malaria. Several points are of interest: For diagnosis both thin and thick smears are recommended; if after a fifteen minute examination parasites are not seen in properly prepared slides further search is not worth while. The use of provocatives to contract the spleen or to induce relapse has not been successful in Boyd's experience. He deplores the fact that many physicians still rely on clinical symptoms and signs for diagnosis, as emphasized by the Fondes several years ago. While some experts are often correct, such evidence has no doubt resulted in ascribing to malaria many conditions not caused by the plasmodia. The three basic symptoms of all forms of malaria are fever, anemia and splenomegaly. Plasmodium falciparum infections give the greatest variety of unusual symptoms. Unfortunately, as is now well known, no drugs available are able to destroy the parasites; their only value is to suppress symptoms.

In observations made by Talbot [208] in a malarious area, Army personnel were given quinacrine hydrochloride prophylactically, while men in the Navy group were given treatment only as symptoms occurred or if parasites were demonstrable in their blood. Blood smears of both groups showed that 48 per cent of those of the Army group and 66 per cent of those of the Navy group contained the organisms. (Among natives 95 per cent had positive smears.) He believes that prophylactic treatment masks the symptoms and permits insidious damage by the plasmodia. It seems better, therefore, to reserve treatment until symptoms with a frank paroxysm occur or until parasitemia is present, unless military necessity requires a maximum of symptomless personnel.

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204. Baker, G. E.: Rocky Mountain Spotted Fever: Nine Year Study of Wyoming Cases, Journal-Lancet **63**:207-213 (July) 1943; Rocky Mountain Spotted Fever, M. Clin. North America **28**:752-778 (May) 1944.

204a. Wolman, M.: Treatment of Typhus with Antityphus Horse Serum, Lancet **2**:210-212 (Aug. 12) 1944.

204b. Yeomans, A.; Snyder, J. C.; Murray, E. S.; Zarafonetis, C. J. D., and Ecke, R. S.: The Therapeutic Effect of Paraaminobenzioc Acid in Louse-Borne Typhus Fever, J. A. M. A. **126**:349-356 (Oct. 7) 1944.

205. Mazzotti, L., and Varela, G.: Natural Infection of Cats with Typhus, Medicina, Mexico **23**:229-235 (June 25) 1943.

206. Beck, M. D.; Bodily, H. L., and O'Donnell, R.: A Strain of Typhus Rickettsia Isolated from the Brain of a Wild Rat in California, Pub. Health Rep. **59**:701-710 (June 2) 1944.

207. Boyd, M. F.: Present Day Problems of Malaria. Infections, J. A. M. A. **124**:1179-1187 (April 22) 1944.

208. Talbot, D. R.: New Aspects of Malaria, J. A. M. A. **123**:192-194 (Sept. 25) 1943.

Similar views are held by Freeborn,[209] who states that any drug used thus far is useless in reducing the infection rate. He discusses in particular the problems created by returning malaria carriers. It is obviously impossible to quarantine all returned military personnel to rule out malaria; even if it were possible, a certain proportion of infected persons would be undetected anyway. To attack the problem it would seem best to adopt the proposal of Williams, to use antianopheline measures in the centers of easiest transmission, namely, in present known endemic foci, and to train antianopheline units to be ready to suppress explosive outbreaks by such measures if they occur elsewhere. While there are potential anopheline vectors of malaria in every state in the union, and probably many human carriers as well, malaria occurs only in a few states where all conditions are favorable to its perpetuation. Therefore, because of unfavorable temperature, humidity, access to carrier and other factors, malarial outbreaks elsewhere can perhaps be easily stopped.

According to two observers,[210] plasmodia were discovered in the blood of Italian prisoners of war in a camp in the United States many months after they had been removed from malarial zones abroad. Eighty-three per cent of those whose blood was found to contain plasmodia and 59 per cent of men in whom malaria developed here apparently had not had the disease before. Absence of demonstrable plasmodia in the blood is no guarantee that malaria will not develop. Chemoprophylaxis may lengthen the incubation period; symptoms do not necessarily appear shortly after prophylactic treatment is stopped.

It has been shown by tests [211] that the hepatic dysfunction probably results from specific injury in most cases of malaria. With the evidence at hand, therapy in the form of high protein, high carbohydrate and vitamin diets is needed during the disease.

Rhesus monkeys infected with Plasmodium knowlesi were treated with sodium sulfathiazole to sterilize the infection.[212] To test the immunity evoked by the infection they were then reinoculated. Evidently no immunity developed, since the usual disease developed in both of them. In monkeys which survived acute infection with aid of immune serum or quinine, partial immunity occurred, which lasted about a year after sterilization of the infection with sodium sulfathiazole.

The value of sulfonamide compounds in the treatment of malaria is uncertain, although Johnson [213] regards sulfadiazine as an effective antimalarial drug. Three relapses occurred in 13 treated patients.

Trichinosis.—According to further studies by Wright and his associates,[214] the distribution of trichinosis in the United States is uniform in degree regardless of geography, occupational, social, racial or environmental factors. The control of the disease, therefore, is not a local matter but a problem of national importance best managed by a federal agency. It may be recalled here that 16 per cent of samples of tissue from over 5,000 persons contained trichinas.

Leptospirosis.—In discussing the clinical features of 15 cases of leptospirosis Bruno and his associates [215] point out how difficult it may be to diagnose the disease even in "typical" cases unless the condition is in mind and proper laboratory tests are made. It is perhaps most easily mistaken for catarrhal jaundice, typhus, malaria, toxic hepatitis, yellow fever and obstructive jaundice with cholecystitis. Diagnosis is even more difficult in the preicteric stage or in cases without icterus in which pneumonia or hepatitis secondary to pneumonia may be suspected, especially if sulfonamide compounds have been used therapeutically.

A case of infection with Leptospira canicola was reported in which differentiation was made from infection with Leptospira icterohaemorrhagiae because the agglutination titer in the serum was a hundred times higher for the former antigen than for the latter.[216] It is doubtful if this criterion alone is acceptable for differentiation.

209. Freeborn, S. B.: Problems Created by Returning Malaria Carriers, Pub. Health. Rep. **59**:357-363 (March 17) 1944.

210. Carney, S. P., and Levin, N. B.: Chronic Malarial Parasitemia in Italian Prisoners of War, J. A. M. A. **124**:1048-1049 (April 8) 1944.

211. Mirsky, I. A.; Brecht, R., and Williams, L. D.: Hepatic Dysfunction in Malaria, Science **99**:20-21 (Jan. 7) 1944.

212. Maier, J., and Coggeshall, L. T.: Duration of Immunity to Plasmodia Knowlesi Malaria in Rhesus Monkeys, J. Exper. Med. **79**:401-430 (April) 1944.

213. Johnson, C. E.: Status of Sulfonamide Therapy in Malaria, Am. J. M. Sc. **206**:327-335 (Sept.) 1943.

214. Wright, W. H.; Jacobs, L., and Walton, A. C.: XVI. Epidemiological Considerations Based on the Examination for Trichinae of 5313 Diaphragms from 189 Hospitals in 37 States and the District of Columbia, Pub. Health Rep. **59**:669-681 (May 26) 1944.

215. Bruno, F. E.; Wilen, C. J. W., and Snavely, J. R.: Spirochetal Jaundice: A Report of Fifteen Cases Including Two Cases of Leptospira Canicola Infection, J. A. M. A. **123**:519-524 (Oct. 30) 1943.

216. Tievsky, G., and Schaefer, B. G.: Canicola Fever (Leptospirosis Canicola): Report of Human Case and Review of Literature, M. Ann. District of Columbia **13**:11-16 (Jan.) 1944.

Hamsters are well suited to experimental studies of leptospirosis.[217] They are susceptible to infection with both L. icterohaemorrhagiae and L. canicola and should be of value in the isolation and identification of the micro-organisms. Specific immune rabbit serum protects hamsters against infection with either, and anticanicola serum is of therapeutic value if given soon after infection with L. canicola.

Relapsing Fever.—In an effort to devise a reliable test for relapsing fever Stein[218] describes a method to obtain spirochetes from the blood by hemolysis with saponin. Antigen made from the spirochetes has broad specificity and can be used for the complement fixation test or for macroscopic agglutination; the former is probably the more reliable.

A case of subacute endocaritis caused by Spirillum minus of rat bite fever is reported.[219] Arsphenamine had no effect on the disease.

Filariasis.—The subject is reviewed by Napier.[219a] In Samoa, microfilarias were demonstrated in the blood of 13 per cent of natives.[220] Many more beyond doubt were infected. Natives were encountered who were in apparent good health with their blood teeming with the organisms; in others with outspoken disease no filarias were found. It was once believed that exposure for years was required before symptoms developed, yet it appears that the disease in a form called *mumu* may develop shortly after exposure to infected mosquitoes. The substance of the worm and the allergic sensitization it provokes are important in the pathogenesis of the disease.

The disfiguring stage of lymphatic obstruction occurs later, and only in exceptional cases. In the United States troops the disease became manifest after five months' residence. Severe constitutional symptoms were rare. Protection against mosquitoes is the best method of prevention.

Repeated injection of stibamine glucoside (neostam), an antimony compound, appears to be effective[221] in curing rats infected with a filarial worm, Litmosoides carinii. Experimental chemotherapy with neostam may be advisable for filariasis of man. Successful results in treatment are recorded after the use of lithium antimony thiomalate (anthiomaline).[221a]

Pinta, a nonvenereal spirochetal disease with striking cutaneous and systemic lesions, found chiefly in Central and South America, has been recognized in the United States.[222]

Miscellaneous Studies.—In one editorial,[223] the work of Mills and Cottingham is said to be "a pioneer contribution to basic immunologic theory." This may be so, but, after all, the degree of phagocytosis in animals fed a diet deficient in vitamins and protein can hardly be considered as the *only* important change which occurs to account for increased susceptibility to infection. The importance of phagocytosis in combating infection has been exaggerated simply because leukocytes can be counted and observed. Many other more subtle changes undoubtedly occur. The conclusions arrived at in this research are contrary to those discussed on page 293 in which animals on a deficient diet were more resistant to infections than those receiving adequate food. In other studies[224] rabbits kept in a condition of hypothermia for ninety-six hours were much less resistant to infection with type III pneumococci than were normal ones, yet no change in the number of leukocytes or in their phagocytic function was demonstrable.

According to a current review,[224a] vitamin deficiency as a factor in susceptibility to infection is not a general epidemiologic principle. Apparently a deficiency of certain vitamins may affect the susceptibility to certain types of infection, but only in unusual instances in which the deficiency is of such severity as to cause changes in the tissues which then become favorable sites for the invasion of micro-organisms. There is no justification for calling vitamin A the "antiinfection" vitamin.

217. Larson, C. L.: Experimental Leptospirosis in Hamsters (Cricetus Auratus), Pub. Health Rep. **59**: 522-527 (April 21) 1944.

218. Stein, G. J.: The Serological Diagnosis of Relapsing Fever, J. Exper. Med. **79**:115-128 (Jan.) 1944.

219. Hitzig, W. M., and Liebesman, A.: Subacute Endocarditis Associated with Infection with a Spirillum, Arch. Int. Med. **73**:415-424 (May) 1944.

219a. Napier, E.: Filariasis Due to Wucheria Bancrofti, Medicine **23**:149-179 (May) 1944.

220. Dickson, J. G.; Huntington, R. W., and Eichold, S.: Filariasis in Defense Force, Samoan Islands, U. S. Nav. M. Bull. **41**:1240-1251 (Sept.) 1943. Huntington, R. W.; Fogel, R. H.; Eichold, S., and Dickson, J. J.: Filariasis Among American Troops in South Pacific Island Group, Yale J. Biol. & Med. **16**:528-537 (May) 1944.

221. Culbertson, J. T., and Rose, H. M.: Chemotherapy of Filariasis in the Cotton Rat by Administration of Neostam, Science **99**:245 (March 24) 1944.

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